Specification.

Diazepane derivatives or salts thereof

The field of technology.

This invention relates to novel diazepane derivatives or salts thereof useful as drug, in particular as activated blood coagulation factor X inhibitor, and the drug thereof.

Background technology.

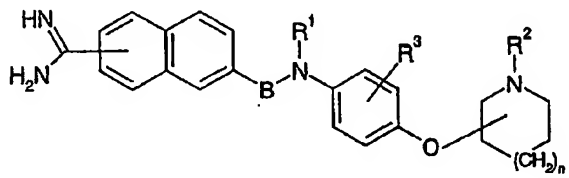
In recent years, accompanied by the Westernisation of the life style and increase in elderly population, thrombotic obstructive diseases such as myocardial infarction, cerebral thrombosis, peripheral arteriothrombosis are on the increase year by year, and the social importance of its treatment is becoming more and more important. Anticoaglulant therapy is one of the internal medical therapy of the treatment and prevention of thrombosis together with the fibriolysis therapy and anti-platelet therapy (Sogo Rinsyo 41: 2141-2145, 1989). In particular, for the prevention of thrombosis, the safety that can withstand the long term administration and expression of concrete and also appropriate anticoagluant activity are essential. Potassium warfarin is widely used all over the world as the only oral anticoagulant, however, because of the properties based on its action mechanism, the control of the anticoagulant ability is difficult (J. Clinical Pharmacology, 32, 196-209, 1992 and N. Eng. J. Med. 324 (26) 1865-1875, 1991), and it is a drug very difficult to use clinically, and emergence of more useful and easy to use anticoagulant is desired.

Thrombin not only controls the conversion of fibrinogen to fibrin which is the final stage of coagulation, but also is deeply involved in the activation and aggregation of platelet (Satoru MATSUO ed., T-PA and Pro-UK, Gakusai Kikaku, pp. 5-40, Blood coagulation, 1986), and its inhibitor has been in the centre of the anticoagulant research for a long time as the target for drug creation. However, the bioavailability for oral administration is low, and there is also a problem in the safety aspect (Biomed. Biochim. Acta, 44, 1201-1210, 1985), and thrombin inhibitor that can be orally administered is not available on the market at present.

The Activated blood coagulation factor X is a key enzyme positioned at the confluence point of the exogenous and endogenous coagulation cascade reaction, and because it is positioned at the upstream of thrombin, it is possible that the inhibition of this factor is more efficient than inhibition of thrombin and also the coagulation system can be specifically inhibited (Thrombosis Research (19), 339-349, 1980).

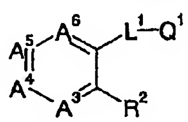
As compound showing activated blood coagulation factor X inhibitory action, amidinonaphthylalkylbenzene derivatives or salts thereof are known (Kokai 5-208946, Thrombosis Haemostasis 71(3), 314-319, 1994 and Thrombosis Haemostasis 71(3), 393-396, 1994).

Moreover, in WO96/16940, amidinonaphthyl derivatives or salts thereof represented by the following general formula are described as compounds showing activated blood coagulation factor X inhibitory action (prior art technology 1).



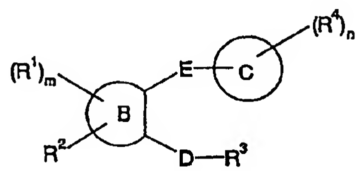
(cf. the specification for symbols in the formula)

Moreover, in WO99/00121, WO99/00126, WO99/00127, WO99/00128, WO00/39111, WO00/39117 and WO00/39118, phenylenediamide compounds and the like represented by the following general formula are described as factor Xa inhibitor (prior art technology 2).



(cf. the specification for symbols in the formula)

Furthermore, in WO99/32477, a wide ranging compounds represented by the following general formula are described as anticoagulant (prior art technology 3).

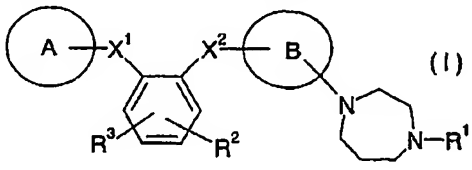


(cf. the specification for symbols in the formula)

Indication of Invention

The inventors of this invention created the diazepane derivatives or salts thereof represented by the following general formula (I), and discovered that these had excellent activated blood coagulation factor X inhibitory action, in particular had excellent per oral activity.

In other words, this invention relates to diazepane derivatives or salts thereof represented by the following general formula (I), and drug composition having these as effective component, in particular an activated blood coagulation factor X inhibitor.



(I)

(The symbols in above formula have the following meanings.

A ring and B ring: may be the same or different and denote aryl or heteroaryl each of which may have 1-3 substituents,

X1: -C(=O)=NR4-, -NR4-C(=O)-, -NR4-CH2-, -O-CH2-, -CH2-CH2, or -CH=CH-,

X2: -C(=O)=NR5-, or -NR5-C(=O)-,

R1: hydrogen atom, lower alkyl, -lower alkylene-O-lower alkyl, C3-8 cycloalkyl, aryl, heteroaryl, -lower alkylene-C3-8 cycloalkyl, -lower alkylene-aryl, -lower alkylene-heteroaryl, or -C(=NR6)-lower alkyl,

R2: -OH, -O-lower alkyl, -O-lower alkylene-OH, -O-SO2-OH, -O-lower alkylene-COOH, O-lower alkylene-COO-lower alkyl, -COOH, -COO-lower alkyl, or halogen atom,

R3: hydrogen atom, halogen atom, or lower alkyl,

R4, R5, and R6: may be the same or different and denote hydrogen atom, or lower alkyl)

The compound of this invention (I) differs from the structure of the compound described in prior art technology 1, for the point of having diazepan-1-yl group, the point of having at least 4 ring structure, the point in which the nitrogen atom of diazepane is directly bonded to the B ring, and the like. Moreover, the compound of this invention (I) differs from the structure of the compound described in prior art technology 2, for the point of having diazepan-1-yl group. Furthermore, in the prior art technology 3, no compound having diazepan-1-yl group is described in embodiments. in other words, the chemical structural characteristics of the compound of this invention (I) is that the diazepanylaryl or diazepanylheteroaryl is bonded to benzene ring via amide bond and the like, and also said benzene ring is bonded to aryl or heteroaryl via abide bond and the like, and also said benzene ring has -OH, -O-lower alkyl, or halogen and the like.

Below, the compound of this invention (I) is described in detail.

In the definition of general formula in this specification, the term "lower" means a straight chain or branched carbon chain of carbon number 1-6 unless specifically stated. Accordingly, as lower alkyl in R1-R6 and substituent exemplified later, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, hexyl, isohexyl, 1-methylpenttyl, 2-methylpenttyl, 3-methylpenttyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1,3-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-1-methylpropyl, 1-ethyl-2-methylpropyl, and the like are nominated. Among these, ones having carbon number 1-3 are preferred, and methyl and ethyl are particularly preferred.

The "lower alkylene" denotes C1-6 alkylene wherein an arbitrary hydrogen atom is removed from aforesaid "lower alkyl", and methylene, ethylene, propylene, isopropylene are preferred.

The "aryl" means aromatic hydrocarbon ring including condensed ring, preferably aryl of carbon number 6-14, more preferably phenyl, naphthyl and the like are nominated.

The "heteroaryl" means heterocyclic aryl including condensed ring having 1-4 hetero atms which may be the same or different and selected from N, S and O, and in embodiments, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, isothiazolyl, isoxazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, indolyl, indazolyl, indolizinyl, quinolyl, isoquinolyl, quinazolinyl, quinolidinyl, quinoxalinyl, cinnolinyl, benzimidazolyl, imidazopyridyl, benzofuranyl, dihydrobenzofuranyl, naphthylidinyl, 1,2-benzoisoxazolyl, benzoxazolyl, benzothiazolyl, oxazolopyridyl, isothiazolopyridyl, benzothienyl and the like are nominated, however it is not limited to these.

The "C3-8 cycloalkyl" denotes cycloalkyl of carbon number 3-8, and in particular, cyclopropyl and cyclobutyl are preferred.

As "substituent" of the "aryl or heteroaryl each of which may have 1-3 substituents", optionally substituted lower alkyl, lower alkenyl, lower alkynyl, C3-8 cycloalkyl, -O-optionally substituted lower alkyl, halogen atom, -NH2, -NH-lower alkyl, -N-(lower alkyl)2, -C(=NH)-NH2, -C(=N-OH)-NH2, -C(=NH)-NH-OH, -C(=NH)-NH-C(=O)-O-lower alkyl, -COOH, -C(=O)-O-optionally substituted lower alkyl, -C(=O)-O-optionally substituted C6-14 aryl, -C(=O)-O-optionally substituted heteroaryl, -CN, -NO2, -OH, -O-CO-optionally substituted lower alkyl, -O-CO-NH2, -O-CO-NH-

lower alkyl, -O-CO-N-(lower alkyl)2, -SH, -C(=O)-NH2, -C(=O)-NH-(lower alkyl), -C(=O)-N-(lower alkyl)2 and the like are nominated.

As "substituent" of the "optionally substituted lower alkyl, lower alkenyl, lower alkynyl, C3-8 cycloalkyl", "optionally substituted C6-14 aryl", or "optionally substituted heteroaryl", halogen atom, -COOH, -C(=O)=O+lower alkyl, -OH, -NH2, -NH-lower alkyl, -N-(lower alkyl)2 and the like are nominated. As "halogen atom", fluorine atom, chlorine atom, iodine atom, bromine atom are nominated. In particular, chlorine atom and bromine atom are preferred.

Moreover, as R1, a lower alkyl is preferred, in particular methyl is preferred. As R2, -OH is in particular preferred. R4-R6 may be the same or different and denote hydrogen atom or lower alkyl, however, hydrogen atom is more preferred. Moreover, as X1, -C(=O)-NR4-, -NR4-C(=O)-, -NR4-CH2- and -O-CH2-are preferred, and -C(=O)-NR4- and -NR4-C(=O)- are particularly preferred. X2 denotes -C(=O)-NR5- or -NR5-C(=O)-, and -NR5-C(=O)- is more preferred.

The A ring and B ring may be the same or different and preferably benzene ring, pyridine ring, naphthalene ring, thiophene ring, benzofuran ring or quinoline ring. In particular, benzene ring is preferred.

Among the compounds of this invention, the embodiments of particularly preferred compounds are 3-hydroxy-4'-methoxy-2-{[4-(4-methyl-1,4-diazepan-1-yl) benzoyl] amino} benzanilide, 3-hydroxy-N1-(4-methoxybenzoyl)-N2-[4-(4-methyl-1,4-diazepan-1-yl) benzoyl]-1,2-phenylenediamine, 5-chloro-N-(5-chloro-2-pyridyl)-3-hydroxy-2-{[4-(4-methyl-1,4-diazepan-1-yl) benzoyl] amino} benzamide, 5-chloro-3-hydroxy-4'-methoxy-2-{[4-(4-methyl-1,4-diazepan-1-yl) benzoyl] amino} benzanilide and 5-bromo-N-(5-chloro-2-pyridyl)-3-hydroxy-2-{[4-(4-methyl-1,4-diazepan-1-yl) benzoyl] amino} benzamide or salts thereof.

Moreover, mixture of geometric isomer, tautomer, various isomers such as optical isomers and isolated one are included in the compound of this invention.

There is a situation that the compound of this invention (I) forms acid addition salt. Moreover, there is a situation depending on kind of substituent that a salt with a base is formed. As such salt, in embodiments, acid addition salts of mineral acid such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulphuric acid, nitric acid, phosphoric acid and the like, organic acid such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid,

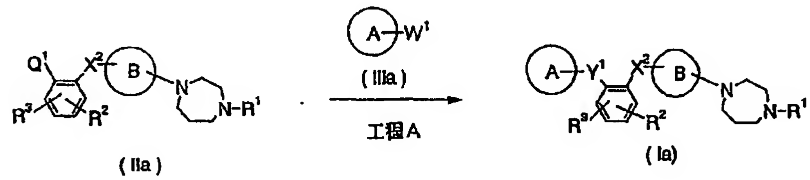
lactic acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, ethanesulfonic acid, and the like, acidic amino acid such as aspartic acid, glutamic acid and the like, salt with inorganic base such as sodium, potassium, magnesium, calcium, aluminium and the like, organic base such as methylamine, ethylamine, ethanolamine and the like, basic amino acid such as lysine, ornithines and the like, and ammonium salt and the like are nominated.

Furthermore, a hydrate of the compound (I), pharmaceutically acceptable various solvates and the crystal polymorphism are included in this invention. Moreover naturally this invention is not restricted to the compounds described in later-described Examples but includes all diazepane derivatives represented by the general formula (I) or pharmaceutically acceptable salts thereof.

Moreover the compounds of this invention include all the compound the is converted to compound of aforesaid (I) or a salt thereof by metabolism in vivo, so called prodrug. As the group forming the prodrug of this compound, groups described in Prog. Med. 5: 2157-2161 (1985) and groups described in "Drug development" vol. 7, molecular design pp. 163-198, Hirokawa Shoten (1990) are nominated.

(A process for the production)
Below a typical process for the production of the compound of this invention is described.

Step A



(wherein, A, B, R1, R2, R3 and X2 have aforesaid meanings, and, as for Q1, W1, when Q1 denotes -NHR4, then W1 denotes -COOH, and when Q1 denotes -COOH, then W1 denotes -NHR4. Y denotes -C(=O)-NR4- or -NR4-C(=O)-. R4 has aforesaid meaning.)

<u>Step A</u>
It is a reaction wherein carboxylic acid and the amine in a combination of compound (IIa) and compound (IIIa) are reacted preferably in the presence of condensing agent and the compound (Ia) is synthesised. This reaction can be carried out following acylation reaction of conventional method.

As condensing agent, N,N-dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-(N,N-dimethylamino) propyl) carbodiimide, carbonyldiimidazole, diphenylphosphoryl azide (DPPA) or diethyl phosphoryl cyanide and the like can be suitably used.

Moreover, carboxylic acid is derived to corresponding active derivative of carboxylic acid, thereafter it can be condensed with amine.

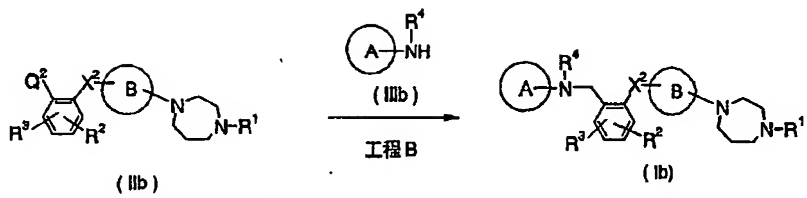
As active derivative of carboxylic acid to be used, active ester obtained by reaction with the compound of phenolic system of for example p-nitrophenol and the like, the compound of N-hydroxyamine system of for example 1-hydroxy succinimide, 1-hydroxybenzotriazole and the like; carbonic acid mono alkyl ester or mixed acid anhydride obtained by reaction with organic acid or phosphoric acid system mixed acid anhydride obtained by reaction with diphenylphosphoryl chloride, N-methylmorpholine; acid azide obtained by reaction of ester with hydrazine, alkyl nitrite; acid halide of for example acid chloride, acid bromide and the like; symmetric acid anhydride and the like are nominated. Usually aforesaid reaction is performed in a solvent under cooling to room temperature, however, there may be a situation that it must be carried out under anhydrous conditions depending on the acylation reaction.

As solvent, a solvent which does not participate in reaction, for example water, ethanaol, methanol, dimethylformamide, dioxane, tetrahydrofuran, ether, dichloroethane, dichloromethane, chloroform, carbon tetrachloride, dimethoxymethane, dimethoxyethane, ethyl acetate, benzene, acetonitrile, dimethylsulfoxide and the like or mixed solvent of these can be used, and it is preferably selected according to the applied process.

Moreover, depending on the applied process, there is a situation that the reaction proceeds smoothly by reacting in the presence of base such as sodium carbonate, potassium carbonate, sodium ethoxide, potassium t-butoxide, 1,8-diazabicyclo [5.4.0] undec-7-ene (DBU), N-methylmorpholine, triethylamine, trimethylamine, pyridine, sodium hydride, butyllithium, sodium amide and the like or using these base as solvent.

Moreover, any method for the reaction for the formation of amide bond can be employed other than the method described here.

Step B



(wherein, A, B, R1, R2, R3, R4 and X2 have aforesaid meanings, and, Q2 denotes -CHO or -CH2-leaving group. As leaving group, halogen group, -O-(SO2)-alkyl, -O-(SO2)-aryl group and the like are nominated.)

Step B

It is a reaction wherein aldehyde and amine or a compound having -CH2-leaving group and amine in a combination of compound (IIb) and compound (IIIb) are condensed and the compound (Ib) is synthesised.

In the case of the combination of aldehyde and amine, this reaction can be carried out in accordance with conventional reductive amination in the presence of reducing agent.

As reducing agent, sodium borohydride, sodium cyanohydride, sodium triacetoxyborohydrate, borane-trimethylamine complex and the like can be suitably used. Moreover, catalytic hydrogenation may be carried out in the presence of catalyst such as palladium-carbon, platinum oxide and the like at ambient pressure to increased pressure. This reaction is carried out in a solvent which is not involved in aforesaid reaction under cooling to warming.

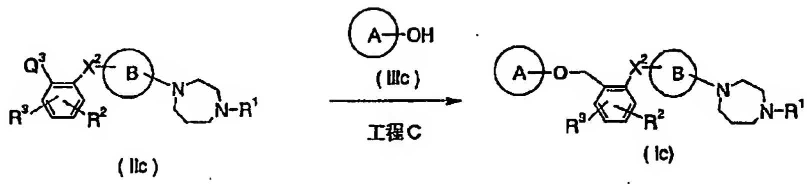
Moreover, depending on the applied process, there is a situation that the reaction proceeds smoothly by reacting in the presence of acid such as acetic acid, toluene sulphonic acid, sulphuric acid and the like or using these as solvent.

In the case of the combination of a compound having -CH2-leaving group and amine, this reaction can be carried out in accordance with well known N-alkylation reaction.

This reaction is carried out in a solvent which is not involved in aforesaid reaction under cooling to warming. Moreover, depending on the applied process, there is a situation that the reaction proceeds smoothly by reacting in the presence of aforesaid base, or using these base as solvent.

Moreover, any method for the reaction for the formation of bond of -NR4-CH2- can be employed other than the method described here.

Step C



(wherein, A, B, R1, R2, R3, and X2 have aforesaid meanings, and, Q3 denotes -CH2-leaving group. As leaving group, halogen group, -O-(SO2)-alkyl, -O-(SO2)-aryl group and the like are nominated.)

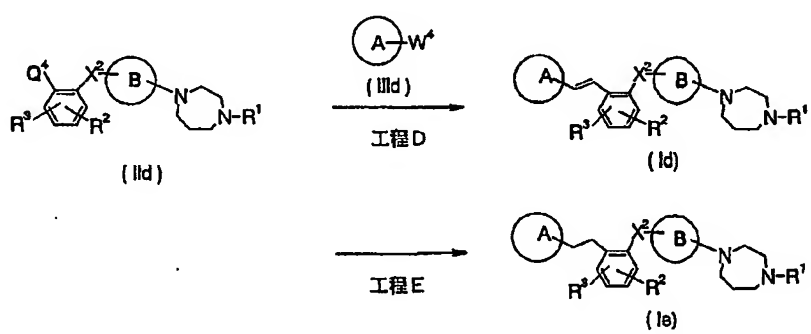
Step C

It is a reaction wherein a compound having -CH2-leaving group and alcohol in a combination of compound (IIc) and compound (IIIc) are condensed and the compound (Ic) is synthesised. This reaction can be carried out in accordance with well known O-alkylation reaction.

This reaction is carried out in a solvent which is not involved in aforesaid reaction under cooling to warming. Moreover, depending on the applied process, there is a situation that the reaction proceeds smoothly by reacting in the presence of aforesaid base, or using these base as solvent.

Moreover, any method for the reaction for the formation of ether bond can be employed other than the method described here.

Step D



Step E

(wherein, A, B, R1, R2, R3, and X2 have aforesaid meanings, and, as for Q4, W4, when Q4 denotes -CHO, then W4 is phosphonium slat such as -CH2-P[+]Ph3Br[-] and the like, phosphorous acid diester such as -CH2-P(=O)(-OEt)2 and the like, or phosphine oxide such as -CH2-P(=O)(-Ph)2 and the like, and when W4 denotes -CHO, then Q4 is phosphonium slat such as -CH2-P[+]Ph3Br[-] and the like, phosphorous acid diester such as -CH2-P(=O)(-OEt)2 and the like, or phosphine oxide such as -CH2-P(=O)(-Ph)2 and the like.)

Step D

It is a reaction wherein aldehyde and phosphonium salt, phosphorous acid diester or phosphine oxide in a combination of compound (IId) and compound (IIId) are reacted in the presence of aforesaid base and the compound (Id) is synthesised. This reaction can be carried out in accordance with well known Wittig reaction or Wittig-Horner reaction.

This reaction is carried out in a solvent which is not involved in aforesaid reaction under cooling to warming. Moreover, depending on the applied process, the intermediate ylide is separated and thereafter it is reacted with aldehyde.

Moreover, any method for the reaction for the formation of carbon-carbon double bond can be employed other than the method described here.

Step E

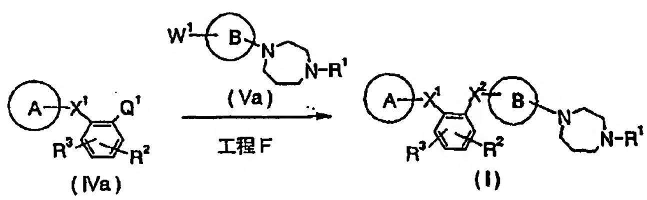
It is a reaction wherein the compound (Ie) is synthesised by reduction reaction of the compound (Id). This reaction can be carried out in accordance with well known hydrogenation reaction using catalyst.

This reaction is carried out under hydrogen atmosphere in a solvent which is not involved in aforesaid reaction under cooling to warming. As catalyst used, palladium-carbon (Pd-C), platinum oxide, Raney nickel, rhodium chlorotriphenylphosphine (Wilkinson catalyst), nickel borate and the like are nominated. Moreover, instead of carrying out under hydrogen atmosphere, ammonium formate, sodium phosphinate, hydrazine and the like can be used as hydrogen source.

Moreover, any method for the reaction for the reduction double bond can be employed other than the method described here.

Moreover, any method for the reaction for the formation of -CH2-CH2 bond can be employed without going through the compound (Id).

Step F



(wherein, A, B, R1, R2, R3, X1, X2, Q1 and W1 have aforesaid meanings.)

Step F

It is a reaction wherein carboxylic acid and amine in a combination of compound (IVa) and compound (Va) are reacted and the compound (I) is synthesised. This reaction is carried out in the same way as in Step A.

Among the compound (I) of this invention, the compound in which the R1 is hydrogen, can also be obtained by carrying out aforesaid hydrogenation reaction and the like using the compound in which R1 in the compound (I) of this invention is benzyl.

Moreover, among the compound (I) of this invention, the compound in which the R1 is other than hydrogen, can also be obtained by carrying out aforesaid well known reductive amination or N-alkylation and the like using the compound in which the R1 in the compound (I) of this invention is hydrogen.

Moreover, among the compound (I) of this invention, the compound in which the R2 is -OH, can also be obtained by synthesising a compound in which its hydroxyl group is protected by a protecting group of phenol, thereafter cleaving by suitable cleaving method for said protecting group. Wherein, the protecting group of phenol is not limited in particular, as long as it is usually used for the protection of phenol, and for example, optionally substituted lower alkyl, aralkyl, tri-lower alkylsilyl, lower alkylcarbonyl, lower alkyloxycarbonyl, sulphonyl and the like are nominated. The "aralkyl" means a group in which hydrogen atom of aforesaid alkyl group is replaced by aryl, and in an embodiment, benzyl, phenylethyl and the like are nominated.

Among the compound (I) of this invention, the compound in which the R2 is -O-lower alkyl, -O-lower alkylene-OH, -O-lower alkylene-COOH, O-lower alkylene-COO-lower alkyl, can be obtained by carrying out aforesaid well known -O-alkylation and the like using the compound in which the R2 in the compound (I) of this invention is -OH. Moreover, the compound in which the R2 in the compound (I) of this invention is -O-SO2-OH can be obtained by sulphonation of the compound in which the R2 in the compound (I) of this invention is -OH using trimethylamine-sulphurtrioxide complex and the like. Furthermore, when an ester group is present in R2, a compound in which the R2 is carboxyl group can be obtained by hydrolysis under acidic condition such as aqueous hydrochloric acid and the like or basic condition such as aqueous sodium hydroxide and the like.

Among the compound (I) of this invention, the compound in which A ring has hydroxyamidino group or amidino group can be obtained using a compound in which the A ring in the compound (I) of this invention has nitrile group. This reaction is carried out in a solvent which is not involved in aforesaid reaction under cooling to warming. Moreover, depending on the applied process, there is a situation that the reaction proceeds smoothly by reacting in the presence of aforesaid base, or using these base as solvent.

As synthesis method of the compound in which A ring has amidino group, the methods shown in the following (i) to (iv) are nominated.

(i) Method in which nitrile is imidated, thereafter, it is condensed with amine:
Alcohol such as methanol, ethanol and the like is acted on a compound in which the A ring in the compound (I) of this invention has nitrile group in the presence of hydrochloric acid gas at -40 degrees to 0 degrees, thereby imidate is formed, thereafter, it is reacted with amine or amine salt such as ammonia, ammonium carbonate, ammonium chloride, ammonium acetate and the like. As solvent, a solvent which is not involved in aforesaid reaction can be used.

(ii) Method in which nitrile is converted to thioamide thereafter thioimidate is formed, and condensed with amine:
The compound in which the A ring in the compound (I) of this invention has nitrile group is reacted with hydrogen sulphide in the presence organic base such as methylamine, triethylamine, pyridine, picoline and the like, or the compound in which the A ring in the compound (I) of this invention has nitrile group is reacted with dithiophosphoric acid O,O-diethyl in the presence of hydrogen chloride, thereby thioamide body is obtained.

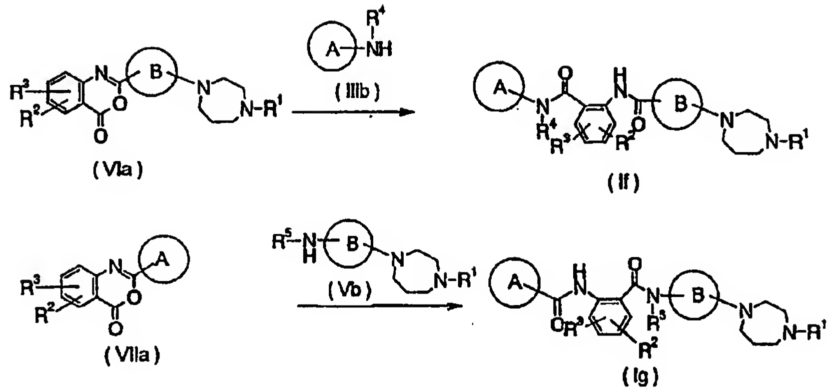
Next, lower alkyl halide such as methyl iodide, ethyl iodide and the like is reacted with aforesaid thioamide body, and thioimidate body is formed, thereafter, it is reacted with amine or amine salt such as ammonia, ammonium carbonate, ammonium chloride, ammonium acetate and the like. As solvent, a solvent which is not involved in aforesaid reaction can be used.

(iii) Method in which amine, amine salt, metal amide, Grignard reagent is directly added to the nitrile:
Reagent such as ammonia, ammonium chloride and ammonia, ammonium thiocyanate, alkylammonium thiocyanate, NaNH2, (CH)2NMgBr and the like is directly added to the compound in which the A ring in the compound (I) of this invention has nitrile group. As solvent, a solvent which is not involved in aforesaid reaction can be used. Or, the reaction can be carried out without solvent.

(iv) Method in which hydroxyamidino group is reduced:
Using the compound in which the A ring in the compound (I) of this invention has nitrile group, aforesaid hydrogenation reaction is carried out directly, or acetic acid or trifluoroacetic acid is acted using acetic acid, trifluoroacetic acid and the like as solvent, thereafter, aforesaid hydrogenation reaction is carried out, thereby hydroxyamidino group can be reduced.

Moreover, any method for the reaction for the formation of amidine group can be employed other than the method described here.

The compound represented by general formula (I) can be produced by arbitrary combination of the steps which can be adopted by person skilled in the art such as alkylation, acylation, oxidation, reduction, hydrolysis and the like. Moreover, the method shown in the following reaction equations is in particular effective for the synthesis of the compound represented by the general formula (I).



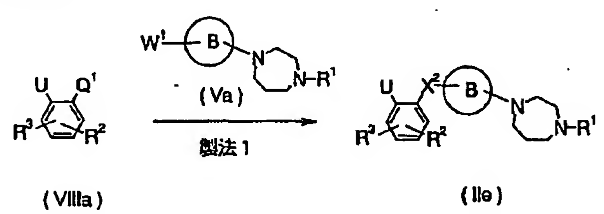
(wherein, A, B, R1, R2, R3, R4 and R5 have aforesaid meanings).

It is a reaction in which compound (VIa) and amine (IIIb) or compound (VIIa) and amine (Vb) are reacted thereby amide bond is formed and compound (If) or compound (Ig) is obtained, it is carried out in aforesaid inert solvent, at room temperature to warming. Moreover, depending on the applied process, there is a situation that the reaction proceeds smoothly by reacting in the presence of base such as N-methylmorpholine, triethylamine, trimethylamine, pyridine, sodium hydride, potassium-t-butoxide, butyllithium, sodium amide and the like or using these base as solvent.

(a production method of starting material compound)

Hereinafter, a typical process for the production of the starting material compound of the compound of this invention (I) is described.

Production method 1



(wherein, B, R1, R2, R8, Q1, W1 and X2 have aforesaid meanings, U denotes -COOH, -NHR5, -CH2-leaving group, -CHO, phosphonium slat such as -CH2-P[+]Ph3Br[-] and the like, phosphorous acid diester such as -CH2-P(=O)(-OEt)2 and the like, or phosphine oxide such as -CH2-P(=O)(-Ph)2 and the like. R5 has aforesaid meaning)

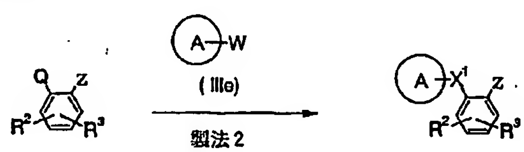
<u>Production method 1</u>

It is a reaction in which carboxylic acid and amine in a combination of compound (VIIIa) and compound (Va) are condensed, and amide bond is formed. This reaction is carried out in the same way as in aforesaid Step A.

Moreover, when U in compound (IIe) denotes -CH2-leaving group, the compound in which U is -CHO can be obtained by oxidation reaction using 4-methylmorpholine N-oxide and the like, and the compound in which U is phosphonium salt of for example -CH2-P[+]Ph3Br[-]can be obtained by reaction organophosphorous compound of for example triphenylphosphine and the like.

Moreover, the compound represented by general formula (IIe) can be produced by arbitrary combination of the steps which can be adopted by person skilled in the art such as alkylation, acylation, oxidation, reduction, hydrolysis and the like. For example, the compound having -NO2 at the site corresponding to U is obtained, thereafter aforesaid reduction reaction such as hudrogenation reaction is carried out, and the compound in which U is NH2 can be obtained. Moreover, the compound having ester group at the site corresponding to U is obtained, thereafter it is hydrolysed under acidic conditions using aqueous hydrochloric acid and the like or basic conditions using sodium hydroxide, and the compound in which U is -COOH can be obtained. Further, using the compound having amino group protected with t-butoxycarbonyl group or benzyl group, it is cleaved by the suitable process for cleaving each protecting group such as acidic conditions using trifluoroacetic acids and the like or reducing conditions of aforesaid hydrogenation, thereby the compound in which U is -NHR5 can be obtained.

Production method 2



(VIIIb) (IVb)

(wherein, A, R2, R3 and X1 have aforesaid meanings. Z denotes -COOH, -NHR5.
As for Q, W, when Q denotes Q1 then W denotes W1, and when Q denotes Q2 then W denotes -NHR4, and when Q denotes Q3 then W denotes -OH, and when Q denotes Q4, W denotes W4. Q1, Q2, Q3, Q4, W1, W4, R4 have aforesaid meanings.)

<u>Production method 2</u>.

When Q denotes Q1 and W denotes W1, it is a reaction in which carboxylic acid and the amine in a combination of compound (IIIe) and compound (VIIIb) are reacted and the compound (Ivb) is synthesised. This reaction can be carried out by the same process as step A.

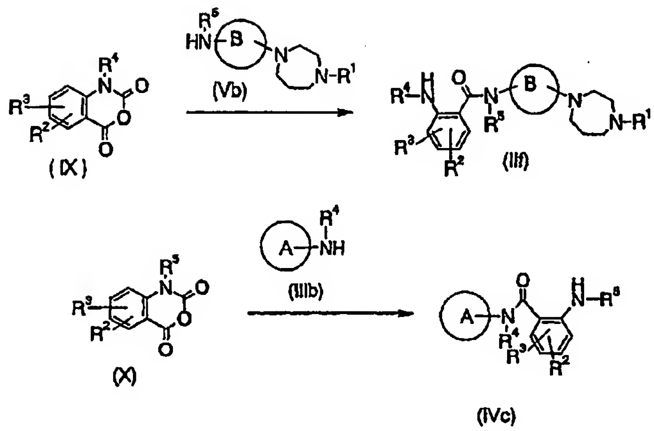
When Q denotes Q2 and W denotes -NHR4, it is a reaction in which aldehyde and amine or the compound having -CH2-leaving group and amine in a combination of compound (IIIe) and compound (VIIIb) are condensed, and the compound (IVb) is synthesised. This reaction can be carried out by the same process as step B.

When Q denotes Q3 and W denotes -OH, it is a reaction in which the compound having -CH2-leaving group and alcohol in a combination of compound (IIIe) and compound (VIIIb) are condensed, and the compound (IVb) is synthesised. This reaction can be carried out by the same process as step C.

When Q denotes Q4 and W denotes W4, it is a reaction in which aldehyde and phosphonium salt, phosphorous acid diester or the phosphine oxide in a combination of compound (IIIe) and compound (VIIIb) are condensed, and the compound (IVb) is synthesised. This reaction can be carried out by the same process as step D.

Moreover, the compound represented by general formula (IVb) can be produced by arbitrary combination of the steps which can be adopted by person skilled in the art such as alkylation, acylation, oxidation, reduction, hydrolysis and the like. For example, a compound having -NO2 at the site corresponding to Z is obtained, thereafter the compound in which Z is -NH2 can be obtained by reduction reaction such as aforesaid hydrogenation reaction. Moreover, the compound having ester group at the site corresponding to Z is obtained, thereafter it is hydrolysed under acidic conditions using aqueous hydrochloric acid of basic conditions using sodium hydroxide and the like, and the compound in which Z is -COOH can be obtained. Further, using the compound having amino group protected with t-butoxycarbonyl group or benzyl group at the site corresponding to Z, it is cleaved by the suitable process for cleaving each protecting group such as acidic conditions using trifluoroacetic acids and the like or reducing conditions of aforesaid hydrogenation, thereby the compound in which Z is -NHR5 can be obtained.

Moreover, the process shown in the following reaction equation is in particular effective for the synthesis of the compound represented by general formula (IIf), (IVc).



(wherein, A, B, R1, R2, R3, R4 and R5 have aforesaid meanings).

It is a reaction in which compound (IX) and amine (Vb) or compound (X) and amine (IIIb) are reacted thereby amide bond is formed and compound (IIf) or compound (IVc) is obtained, it is carried out in aforesaid inert solvent, at room temperature to warming. Moreover, depending on the applied process, there is a situation that the reaction proceeds smoothly by reacting in the presence of base such as N-methylmorpholine, triethylamine, trimethylamine, pyridine, sodium hydride, potassium-t-butoxide, butyllithium, sodium amide and the like or using these base as solvent.

The compound of this invention produced in this way can be isolated and refined by using well known method such as extraction, sedimentation, fraction chromatography, fractional crystallisation, recrystallisation and the like. Moreover, as salt of the compound of this invention, desired salt can be derived by subjecting to ordinary salt formation reaction.

Moreover, when the compounds of this invention have asymmetric carbon, optical isomer is present. These optical isomers can be separated by conventional procedures such as fractional crystallisation by recrystallisation with appropriate salt or column chromatography and the like.

<u>Possible applications in industry</u>

The compound of this invention inhibits activated blood coagulating factor X specifically and has a strong anticoagulation action. Accordingly it is useful as a blood clotting inhibitor or a prevention • therapeutic agent of disease caused by thrombosis or embolus.

As aforesaid diseases, diseases caused by cerebral blood vessel damage such as cerebral infarction, cerebral thrombosis, cerebral embolism, transient ischemic attack (TIA), subarachnoid bleeding (angiospasm), ischemic cardiac diseases such as acute and chronic myocardial infarction, unstable angina, coronary artery thrombolysis, diseases caused by lung angiopathy such as pulmonary infarction, lung embolus, furthermore, periphery artery thrombosis, deep vein thrombosis, disseminated intravascular coagulation syndrome, thrombogenesis after artificial blood vessel or synthetic valve implantation, reocclusion and restenosis after coronary artery bypass operation, reocclusion and restenosis after PTCA (Percutaneous transluminal coronary angioplasty), PTCR (Percutaneous transluminal coronary recanalisation) operation, thrombogenesis during extracorporeal circulation or the like are nominated.

Moreover, because the possibility as infection prevention • therapeutic agent of influenza virus on the basis of proliferation inhibiting activity of influenza virus is suggested (Kokai 6-227971) for the compound having activated blood coagulating factor X inhibitory effect, the same effect is expected in the compound of this invention

The excellent activated blood coagulating factor X inhibiting activity of the compound of this invention was confirmed by the following tests.

<u>1) Human activated blood coagulating factor X (human factor Xa) coagulation time measurement.</u>

The agent or physiological saline 10 μl and human factor Xa (Enzyme Research Labs) 50 μl were added to human plasma 90 μl, and it was incubated at 37 degrees for three minutes, and thereafter, 20 mM of CaCl2 100 μl which was warmed to 37 degrees beforehand was added and coagulation time was measured by coagulation meter (Amelung company: KC10). Human plasma was collected from elbow vein of healthy subjects (6 people) by 45 ml using a syringe containing 5 ml of 3.8 % sodium citrate, and the plasma which was separated by centrifugation at 4 degrees /3000 rpm /15 minutes was pooled, cryopreserved and used. Human factor Xa was selected at a concentration in which the coagulation time when physiological saline (control) was added became about 30-40 seconds. The CT2 value (concentration to prolong the coagulation time of control by twice) was determined by plotting the relative value of coagulation time with respect to control (fold) and drug concentration, and by linear regression. The results are shown in the following Table 1.

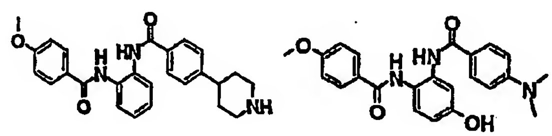
<u>2) Bovine thrombin coagulation time measurement.</u>

The agent or physiological saline 50 μl was added to human plasma 50 μl, and it was incubated at 37 degrees for three minutes, and thereafter thrombin 50 μl warmed to 37 degrees beforehand was

added, and coagulation time was measured by coagulation meter (Amelung company: KC10). Human plasma was collected from elbow vein of healthy subjects (6 people) by 45 ml using a syringe containing 5 ml of 3.8 % sodium citrate, and the plasma which was separated by centrifugation at 4 degrees /3000 rpm /15 minutes was pooled, cryopreserved and used. Thrombin was selected at a concentration in which the coagulation time when physiological saline (control) was added became about 20 seconds. The CT2 value (concentration to prolong the coagulation time of control by twice) was determined by plotting the relative value of coagulation time with respect to control (fold) and drug concentration, and by linear regression. The results are shown in the following Table 1.

Table 1.

	Compound	Human activated blood coagulating factor X coagulation time (CT2) (μM)	Bovine thrombin coagulation time (CT2) (μM)
Example compound	Example 5	0.10	>100
	Example 9	1.71	>100
	Example 11	1.33	>100
	Example 32	1.41	>100
	Example 39	1.53	>100
Control compound	Control 1	17.0	>100
	Control 2	11.3	–



(Control 1) (Example 42 of WO 99/00121)

(Control 2) (Example 198 of WO 99/00121)

3) Enzyme inhibition measurement test by synthetic substrate method.

Reaction buffer (pH 8.4) 80 μl, compound solution 15 μl, synthetic substrate S-2222 (Chromogenix) 2 mM 30 μl were added to 96 well microplate, and human activated blood coagulating factor X (factor Xa Enzyme Research Labs) 0.025 U/ml 25 μl was added and it was reacted at 37 degrees for ten minutes, and thereafter absorbance change at 405 nm was measured with Bio-Rad Company model 3550, and IC50 was calculated. The compound of Example 1 showed IC50 of less than 10 nM or less.

From the results of the measurement of above 1), 2) and 3), it was confirmed that the compound of this invention specifically inhibited human activated blood coagulating factor X and also showed strong anti blood clotting action. For example, the compounds shown in Examples 5, 9, 11, 32 and 39 of this invention prolonged the coagulation time clearly at a lower concentration compared with Example 42 of WO99/00121 (control 1) and same Example 198 (control 2), and it excellent anti blood clotting action was confirmed.

4) ex vivo coagulation time measurement using mouse (oral administration).

The drug dissolved or suspended in 0.5 % methyl cellulose was forcibly orally-administered (10 mg/kg), using oral tube to male ICR mice which was fasted for 12 hours or more (20-30 g, Japan SLC company), and at 30 minutes and two hours later the blood 0.9 ml was collected using the syringe containing 100 μl of 3.8 % sodium citrate from inferior vena cava under diethyl ether anaesthesia , and the plasma was separated by centrifugation at 3000 rpm /10 minutes. Using this plasma, extrinsic system coagulation time (PT) and intrinsinc system coagulation time (APTT) were measured in accordance with the method of the following a) and b).

a) Extrinsic system coagulation time (PT).

Ortho brain thromboplastin (54 mg/vial, freeze-dried preparation, Ortho clinical diagnostics company) was dissolved in Milli-Q water 2.5 ml, and it was preliminary warmed at 37 degrees. Aforesaid plasma 50 μl was warmed to 37 degrees for one minute, and aforesaid thromboplastin solution 50 μl was added, and measurement of coagulation time was carried out. Amelung company KC10A was used for the measurement of coagulation time.

b) Intrinsinc system coagulation time (APTT).

Hemoliance thrombosil I (diayatron company) 50 μl was added to aforesaid plasma 50 μl, and it was warmed to 37 degrees for three minutes, and 50 μl of 20 mM CaCl2 solution preliminary warmed to 37 degrees beforehand was added, and measurement of coagulation time was carried out. Amelung company KC10A was used for the measurement of coagulation time.

Moreover administration dosage or collection of blood time was changed, and dose dependency and change with time of anticoagulation product, was investigated by the same process.

5) ex vivo coagulation time measurement using cynomolgus monkey (oral administration).

After the blood collection before the drug administration, the drug (5 mg/ml) dissolved (suspension) in 0.5 % methyl cellulose was forcibly orally-administered by 2 ml/kg using oral tube to the male

cynomolgus monkey which was fasted for 12 hours or more (around 4 kg in weight) and 1, 2, 4, 6, 8 hours later, blood was collected by 2 ml with 3.8 % sodium citrate 1/10 vol. from femoral vein, the plasma was separated by centrifugation at 3000 rpm /10 minutes. Using this plasma, extrinsic system coagulation time (PT) and intrinsic system coagulation time (APTT) were measured in accordance with the method of aforesaid a) and b). The test was carried out under un-anaesthetised conditions.

As a result of 4) and 5), as for the compound of this invention, prolongation action of coagulation time was observed in oral administration. The compound shown in Example 3 showed coagulation time prolongation action of twice or more in both PT, APTT in both tests of 4) and 5) compared to the control (plasma before drug administration).

The medicinal composition containing as effective ingredient at least one of the compound of this invention represented by the general formula (I) and the pharmaceutically acceptable salt thereof is prepared using a carrier and excipient usually used for formulation, other additives into a tablet, powder, fine granules, granules, capsule agent, pill, liquid agent, injection, suppository, ointment, patch, and is administered aorally or orally.

Clinical dosage with respect to human of the compound of this invention is suitably determined on consideration of the symptoms, body weight, age or gender of the patient, but it is 0.1-500 mg for oral administration and 0.01-100 mg for aoral administration, and this is administered once or divided into several times usually per adult per day. Because the dosage changes under various conditions, there is a case that a smaller quantity than aforesaid dosage range is adequate.

As solid composition for oral administration in accordance with this invention, tablet, powder, granule and the like are used. In such solid composition, at least one active material is mixed with at least one inert diluent, for example lactose, mannitol, dextrose, hydroxypropylcellulose, microcrystalline cellulose, starch, polyvinylpyrrolidone, metasilicate, magnesium aluminate. In accordance with normal methods, the composition may contain additives other than inert diluents, for example lubricant such as magnesium stearate and disintegrating agent such as calcium carboxymethyl cellulose, stabilising agent such as lactose, solubiliser or solubilising agent such as glutamic acid or aspartic acid. A tablet or pill may be film coated in accordance with requirement with sucrose, film of intestine soluble or stomach soluble substance such as gelatin, hydroxypropylcellulose, hydroxypropyl methyl cellulose phthalate.

Liquid composition for oral administration includes pharmaceutically acceptable opacifier, solvent, suspending agent, syrup, elixir agent and the like, and generally used inert diluent, for example purified water, ethanol are included. This composition may contain solubilising agent, solubiliser, wetting agent, adjuvant such as suspending agent, sweetener, flavour agent, aromatic and preservatives besides inert diluent.

As injection agent for aoral administration, sterile aqueous or non-aqueous solvent, suspending agent, opacifier are included. As diluent of aqueous solvent and suspending agent, for example distilled water for injection and physiological saline are included. As diluent of water insoluble solvent and suspending agent, there are for example propylene glycol polyethyleneglycol, vegetable oil such as olive oil, an alcohol such as ethanol, polysorbate 80 (Trade name) and the like.

Furthermore, such composition may include isotonisation agent, preservatives, wetting agent, emulsifier, dispersant, stabilising agent (for example lactose), additive such as solubilising agent or solubiliser. These are sterilised by for example filtration through bacteria retaining filter, formulation of fungicide or irradiation. These and produced as sterile solid composition and dissolved in sterile water or the sterile injectable solvent before use and can be used.

Ideal form for Carrying Out the Invention

Hereinafter, Production Example of the compound of this invention is nominated, and a process for the production of the compound of this invention is described in concrete terms. Moreover the novel compound is contained starting material compound of the compound of this invention, too, and a process for the production of the compound of these is described as Reference Example.

Reference Example 1.

Ethyl 4-bromomethyl-3-nitrobenzoate 26.00 g were dissolved in acetonitrile 90 ml, and 3-aminobenzo nitrile 7.97 g and potassium carbonate 12.44 g were added and the mixture stirred at 70 degrees for three hours. The mixture was cooled to room temperature, and, after filtration, mother liquor was concentrated under reduced pressure. Acetic acid ethyl ester was added to the obtained residue, and it was washed with 1 N aqueous hydrochloric acid, saturated aqueous sodium bicarbonate solution, and thereafter dried with anhydrous magnesium sulphate, and next it was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography with hexane : ethyl acetate (80:20 to 75:25) as elution solvent, and ethyl 4-[(3-cyanophenylamino) methyl]-3-nitrobenzoate 12.06 g was obtained.

Reference Example 2.

Ethyl 4-[(3-cyanophenyl amino) methyl]-3-nitrobenzoate 5.79 g was dissolved in ethanol 50 ml, and purified water 50 ml, ammonium chloride 0.96 g, iron powder 4.97 g were added, and the mixture was heated under reflux for 40 minutes. The reaction liquor was filtered with celite, and it was concentrated under reduced pressure. Acetic acid ethyl ester was added to the obtained residue, and the mixture was washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried with anhydrous magnesium sulphate, and next it was concentrated under reduced pressure, dried, and thereby ethyl 3-amino-4-[(3-cyanophenyl amino) methyl] benzoate 5.71 g was obtained.

Reference Example 3.

Ethyl 4-bromomethyl-3-nitrobenzoate 46.11 g was dissolved in acetonitrile 50 ml and 4-methylmorpholine-N-oxide 20 g was added to this and the mixture was stirred at room temperature for 80 minutes. The reaction liquor was concentrated under vacuum and water was added and it was extracted with chloroform. This organic layer was washed with saturated aqueous sodium chloride solution, and after drying with magnesium sulphate, it was concentrated under vacuum. The obtained residue was purified by silica gel column chromatography hexane : ethyl acetate (4:1), and ethyl 4-formyl-3-nitrobenzoate 10.723 g was obtained.

Reference Example 4.

Ethyl 4-formyl-3-nitrobenzoate 5.81 g was dissolved in toluene 7 ml, and 1,8-diazabicyclo [5.4.0]-undec-7-ene 2.1 ml was added to this and the mixture was stirred at 80 degrees for one hour. 3-[(1,1,1-triphenylphosphonio(?)) methyl] benzonitrile bromide 2.69 g was added to this and the mixture was stirred at 80 degrees for 24 hours. The insolubles were filtered, and the filtrate was concentrated under vacuum. The obtained residue was purified by silica gel column chromatography with hexane : ethyl acetate (10:1) as elution solvent. The obtained intermediate 3.1 g was dissolved in mixed solvent of ethanol 5 ml and tetrahydrofuran 10 ml, and palladium oxide barium sulphate complex 1 g was added to this and the mixture was stirred at room temperature under hydrogen atmosphere for three days. The reaction liquor was filtered with celite, and thereafter the filtrate was concentrated under vacuum. The obtained residue was purified by silica gel column chromatography hexane : ethyl acetate (2:1), and ethyl 3-amino-4-[2-(3-cyanophenyl) ethyl] benzoate 2.35 g was obtained.

Reference Example 5.

3-hydroxy-2-nitro benzoic acid 1.83 g was dissolved in N,N-dimethylformamide 50 ml and 4-methoxyaniline 1.23 g, 1-ethyl-3-dimethylaminopropyl carbodiimide hydrochloride 2.50 g, 1-hydroxybenzotriazole 1.35 g and triethylamine 1.81 ml were added to this and the mixture was stirred at room temperature for 66 hours. The reaction liquor was concentrated under vacuum, and water was added and it was extracted with acetic acid ethyl ester. This organic layer was washed with saturated aqueous sodium chloride solution, and after drying with magnesium sulphate it was concentrated under vacuum. Chloroform was added to the obtained residue, and produced sedimentation was recovered by filtration, and 3-hydroxy-4'-methoxy-2-nitro benzanilide 2.04 g was obtained. The filtrate was purified by silica gel column chromatography with chloroform : methanol (98:2) as elution solvent, and furthermore, chloroform was added to the obtained crude product, and produced sedimentation was recovered by filtration, thereby 3-hydroxy-4'-methoxy-2-nitrobenzanilide 0.24 g was obtained.

Reference Example 6.

3-hydroxy-4'-methoxy-2-nitrobenzanilide 1.15 g was suspended in methanol 50 ml and 10 % palladium-carbon powder 300 mg was added and the mixture was stirred at room temperature under hydrogen atmosphere for one hour. The reaction liquor was filtered with celite and was washed with methanol, and next the filtrate was concentrated under reduced pressure, and 2-amino-3-hydroxy-4'-methoxybenzanilide 966 mg was obtained.

Reference Example 7.

4-(4-methyl-1,4-diazepan-1-yl) benzonitrile 18.86 g was dissolved in 12 N hydrochloric acid 185 ml and the mixture was stirred at 80 degrees for 12 hours, and thereafter it was concentrated under vacuum. Water was added, the mixture was stirred at room temperature, thereafter formed sedimentation was filtered, and it was washed with water. The obtained solid was dried under reduced pressure, and 4-(4-methyl-1,4-diazepan-1-yl) benzoic acid hydrochloride 18.25 g was obtained.

Reference Example 8.

A mixture of 4-(4-methyl-1,4-diazepan-1-yl) benzoic acid hydrochloride 16.3 g, N,N-dimethylformamide 0.88 g, thionyl chloride 14.3 g and ethyl acetate 160 mL was stirred at 40 degrees for three hours and thereafter concentrated under vacuum. A solution of 2-amino-3-nitrophenol 8.35 g, pyridine 9.52 g and acetonitrile 60 mL was added under ice cooling to a mixture of the obtained residue and acetonitrile 130 ml. The mixture was stirred at 5 degrees or less overnight, and thereafter the crystals were recovered by filtration, and 2-amino-3-nitrophenyl 4-(4-methyl-1,4-diazepan-1-yl) benzoate hydrochloride 21.4 g was obtained.

Reference Example 9.

A mixture of 2-amino-3-nitrophenyl 4-(4-methyl-1,4-diazepan-1-yl) benzoate hydrochloride 2.00 g, triethylamine 995 mg and acetonitrile 20 mL was stirred at 70 degrees for 6 hours. A solution of sodium hydroxide 197 mg and water 2 mL was added to the reaction liquor. Water 20 mL was added, thereafter acetonitrile was eliminated by heating and distillation at ambient pressure, and furthermore water 10 mL was added, and the mixture was stirred at room temperature for 14 hours. The precipitated crystals were recovered by filtration, and 2'-hydroxy-4-(4-methyl-1,4-diazepan-1-yl)-6'-nitro benzanilide 1.57 g was obtained.

Reference Example 10.

A mixture of 2'-hydroxy-4-(4-methyl-1,4-diazepan-1-yl)-6'-nitro benzanilide 2.14 g, methanol 43 mL and 10 % palladium-carbon (wet rate 54.2 %) 467 mg was stirred under hydrogen atmosphere at ambient pressure at 30 degrees, till absorption of hydrogen stopped. The catalyst was eliminated by filtration, and the filtrate was concentrated under vacuum. The residue was refined with silica gel chromatography (chloroform : methanol = 20:1 to 10:1), and 2'-amino-6'-hydroxy-4-(4-methyl-1,4-diazepan-1-yl) benzanilide 1.61 g were obtained.

Reference Example 11.

2-amino-3-nitrophenol 308 mg was dissolved in pyridine 10 ml, and 4-methoxybenzoyl chloride 341 mg was added at 0 degrees and the mixture was stirred at room temperature for 18 hours. The reaction liquor was concentrated under reduced pressure, chloroform 20 ml was added to the obtained residue, and it was concentrated under reduced pressure once again. Further this procedure was repeated three times, and the residue from which pyridine was eliminated, was purified by silica gel column chromatography with chloroform as elution solvent, and 2'-hydroxy-4-methoxy-6'-nitro benzanilide 428 mg was obtained. The compound of Reference Example 12 was synthesised in the same way as in Reference Example 6.

Reference Example 13.

3-hydroxy-2-nitro benzoic acid 10.5 g was dissolved in N,N-dimethylformamide 60 ml, and benzyl bromide 15 ml and potassium carbonate 19.0 g were added at 0 degrees, and the mixture was stirred at room temperature overnight. The reaction liquor was filtered with celite, and thereafter it was concentrated under reduced pressure. Water was added to the obtained residue, and it was extracted with ether, thereafter washed with saturated aqueous sodium chloride solution, and dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and benzyl 3-benzyloxy-2-nitrobenzoate 20.7 g was obtained.

Reference Example 14.

Ethanol 100 ml and 1N aqueous sodium hydroxide 120 ml were added to benzyl 3-benzyloxy-2-nitrobenzoate 20.7 g, and the mixture was stirred at room temperature overnight, at 60 degrees for three hours and at 80 degrees for five hours. Ethanol was eliminated by distillation under reduced pressure, and thereafter the obtained aqueous solution was washed with ether, and thereafter hydrochloric acid was added. Produced sedimentation was recovered by filtration, and thereafter it was dried under reduced pressure, and 3-benzyloxy-2-nitro benzoic acid 15.8 g was obtained.

Reference Example 15.

Thionyl chloride 20 ml and several drops of N,N-dimethylformamide were added to 3-benzyloxy-2-nitro benzoic acid 5.47 g, and the mixture was stirred at 80 degrees for 30 minutes. The reaction liquor was concentrated under reduced pressure, and pyridine 35 ml and 2-amino-5-chloropyridine 2.55 g were added to the obtained residue at 0 degrees, and the mixture was stirred at room temperature overnight. The reaction liquor was concentrated under reduced pressure, and saturated aqueous sodium bicarbonate solution was added to the obtained residue, and it was extracted with acetic acid ethyl ester. Organic layer was dried with anhydrous magnesium sulphate, the solvent was eliminated by distillation under reduced pressure, and azeotropic distillation with toluene was carried out, and 3-benzyloxy-N-(5-chloro-2-pyridyl)-2-nitrobenzamide 7.44 g was obtained.

Reference Example 16.

Trifluoroacetic acid 40 ml and pentamethylbenzene 3.72 g were added to 3-benzyloxy-N-(5-chloro-2-pyridyl)-2-nitrobenzamide 7.44 g and the mixture was stirred at 40 degrees overnight. The reaction liquor was concentrated under reduced pressure, and saturated aqueous sodium bicarbonate solution was added to the obtained residue by a degree that was not made alkaline, and it was extracted with acetic acid ethyl ester. The organic layer was extracted with 1N sodium hydroxide aqueous solution,

and thereafter hydrochloric acid was added to the aqueous layer, it was acidified, and it was extracted with chloroform. It was dried with anhydrous magnesium sulphate, next the solvent was eliminated by distillation under reduced pressure, ethanol suspension 200 ml of Raney nickel was added to the obtained residue. The mixture was stirred under hydrogen atmosphere for six hours, thereafter N,N-dimethylformamide was added, and the insolubles were eliminated by filtration. The solvent was eliminated under reduced pressure by distillation, and water was added to the obtained residue. The produced precipitate was recovered by filtration, dried under reduced pressure, and 2-amino-N-(5-chloro-2-pyridyl)-3-hydroxybenzamide 4.58 g was obtained.

Reference Example 17.

2-amino-N-(5-chloro-2-pyridyl)-3-hydroxybenzamide 3.06 g and N-chlorosuccinimide 1.80 g were dissolved in N,N-dimethylformamide 60 ml and the mixture was stirred at 50 degrees for eight hours and at room temperature for four hours, and thereafter the insolubles were eliminated by filtration. The solvent was eliminated under reduced pressure by distillation, and thereafter 1 N aqueous sodium hydroxide was added to the obtained residue, and it was extracted with acetic acid ethyl ester. The organic layer was dried with anhydrous magnesium sulphate, and next the solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined using silica gel column chromatography. Ethanol was added to the obtained crude purified material, and produced precipitate was recovered by filtration, and it was dried under reduced pressure, and 2-amino-5-chloro-N-(5-chloro-2-pyridyl)-3-hydroxybenzamide 767 mg was obtained. Mother liquor was concentrated, ethyl acetate-isopropyl ether was added and the sedimentation produced was recovered by filtration, and thereafter it was dried under reduced pressure, thereby the aforesaid compound was further obtained by 942 mg.

The compounds of Reference Examples 18, 19 were synthesised in the same way as in Reference Example 17.

Reference Example 20.

Ethyl 2-amino-5-chloro-3-hydroxybenzoate 3.23 g was dissolved in 3 N hydrochloric acid solution 160 ml and the mixture was stirred at 85 degrees for three hours and at 80 degrees for five days. The reaction liquor was cooled to room temperature, and thereafter the insolubles were filtered, and 1N aqueous sodium hydroxide 320 ml was added to the filtrate, and the mixture was stirred at room temperature for one hour. The produced precipitate was filtered, and it was washed with purified water, thereafter dried under reduced pressure, and 2-amino-5-chloro-3-hydroxy benzoic acid 1.55 g was obtained.

Reference Example 21.

2-amino-5-chloro-3-hydroxy benzoic acid 1.12 g was dissolved in N,N-dimethylformamide 60 ml and 4-methoxyaniline 7.38 g, 1-ethyl-3-dimethylaminopropyl carbodiimide hydrochloride 1.73 g, 1-hydroxybenzotriazole 1.21 g and triethylamine 1.26 ml were added to this and the mixture was stirred at room temperature for 13 hours. The reaction liquor was concentrated under vacuum, and acetic acid ethyl ester was added to the obtained residue, and it was washed with purified water and saturated aqueous sodium chloride solution, dried with magnesium sulphate, and thereafter it was concentrated under reduced pressure. Chloroform was added to the obtained residue and the mixture was stirred for 30 minutes, and thereafter produced sedimentation was recovered by filtration, and it was washed with chloroform, thereafter dried under reduced pressure, and 2-amino-5-chloro-3-hydroxy-4'-methoxy-2-benzanilide 0.96 g was obtained.

Reference Example 22.

Thionyl chloride 40 ml was added to 4-(4-methyl-1,4-diazepan-1-yl) benzoic acid hydrochloride 5.09 g, and the mixture was stirred at 60 degrees for 30 minutes. The reaction liquor was concentrated under reduced pressure, and it was dried to a solid. A solution of ethyl 3-amino-4-[(3-cyanophenyl amino) methyl] benzoato 5.65 g dissolved in pyridine 50 ml was added to the obtained residue, and the mixture was stirred at room temperature for five hours. The reaction liquor was concentrated under reduced pressure, and thereafter acetic acid ethyl ester and chloroform were added to the obtained residue, and it was washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried with anhydrous magnesium sulphate, and next concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography with hexane : ethyl acetate (95:5 to 90:10) as elution solvent, and ethyl 4-[(3-cyanophenyl amino) methyl]-3-[4-(4-methyl-1,4-diazepan-1-yl) benzoylamino] benzoate 6.42 g was obtained.

The compound of Reference Example 23 was synthesised in the same way as in Reference Example 22.

Example 1.

Ethyl 4-[(3-cyanophenyl amino) methyl]-3-[4-(4-methyl-1,4-diazepan-1-yl) benzoylamino] benzoate 4.09 g was dissolved in ethanol 80 ml, and hydrochloric acid gas was introduced at -20 degrees or less for 20 minutes, thereafter the mixture was warmed to 3 degrees and stirred for 24 hours. The reaction liquor was concentrated under reduced pressure, and dried to a solid, the obtained residue

was dissolved in ethanol 80 ml, and acetic acid ammonia 6.16 g was added and the mixture was stirred at room temperature for 3.5 days. The reaction liquor was concentrated under reduced pressure, the obtained residue was refined by ODS column chromatography with 0.002 N aqueous hydrochloric acid : ethanol (100:0 to 80:20) as elution solvent, thereafter it was freeze-dried, and ethyl 4-[(3-cyanophenyl amino) methyl]-3-[4-(4-methyl-1,4-diazepan-1-yl) benzoylamino] benzoate hydrochloride 3.84 g was obtained. Among the obtained compound, 1.70 g thereof was dissolved in ethanol 20 ml, and 1N aqueous sodium hydroxide 30 ml was added and, the mixture was stirred at room temperature for one hour. The reaction liquor was neutralised with 1 N aqueous hydrochloric acid, and thereafter it was concentrated under reduced pressure. The obtained residue was refined by ODS column chromatography with 0.002 N aqueous hydrochloric acid : acetonitrile (100:0 to 92:8) as elution solvent, and thereafter it was freeze-dried, and 4-[(3-carbamimidylphenyl amino methyl]-3-[4-(4-methyl-1,4-diazepan-1-yl) benzoylamino] benzoic acid hydrochloride 1.48 g was obtained.

Example 2.

Ethyl 4-[(3-cyanophenyl amino) methyl]-3-[4-(4-methyl-1,4-diazepan-1-yl) benzoylamino] benzoate 1.42 g was dissolved in ethanol 30 ml and hydroxylamine hydrochloride 291 mg and triethylamine 0.78 ml were added and the mixture was stirred at 60 degrees for 24 hours. The reaction liquor was concentrated under reduced pressure, the obtained residue was purified by silica gel column chromatography with chloroform : methanol : ammonia water solution (100:0:0 to 92:8:0.8) as elution solvent, and the crude purified material of ethyl 4-({[3-(N-hydroxycarbamimidyl) phenyl] amino} methyl)-3-[4-(4-methyl-1,4-diazepan-1-yl) benzoylamino] benzoate was obtained. Furthermore, it was refined by ODS column chromatography with 0.002 N aqueous hydrochloric acid : methanol (100:0 to 88:12) as elution solvent, thereafter it was freeze-dried, and ethyl 4-({[3-(N-hydroxycarbamimidyl) phenyl] amino} methyl)-3-[4-(4-methyl-1,4-diazepan-1-yl) benzoylamino] benzoato hydrochloride 1.03 g was obtained.

The compounds of Examples 3, 5, 7, 54 were synthesised in the same way as in Example 1.
The compounds of Examples 4, 6, 8, 53 were synthesised in the same way as in Example 2.

Example 9.

4-(4-methyl-1,4-diazepan-1-yl) benzoic acid hydrochloride 812 mg was dissolved in thionyl chloride 8 ml, and the mixture was stirred time at 60 degrees for 30 minutes. The reaction liquor was concentrated under reduced pressure, and it was dried to a solid. A solution of 2-amino-4'-methoxy-3-hydroxy benzanilide 774 mg dissolved in pyridine 15 ml was added to the obtained residue at 0 degrees and it was stirred at room temperature for two hours. The reaction liquor was concentrated

under reduced pressure, thereafter toluene was added to the obtained residue, and it was concentrated under reduced pressure once again. Saturated aqueous sodium bicarbonate solution and acetic acid ethyl ester were added to the obtained residue, and the obtained sedimentation was recovered by filtration. Ethyl acetate layer of the mother liquor was dried with anhydrous sodium sulphate, and thereafter it was concentrated under reduced pressure. The obtained residue and sedimentation recovered by filtration were mixed, and it was purified by silica gel column chromatography with chloroform : methanol (98:2) as elution solvent, and 3-hydroxy-4'-methoxy-2-{[4-(4-methyl-1,4-diazepan-1-yl) benzoyl] amino} benzanilide was obtained 873 mg. The obtained compound was suspended in ethanol 10 ml and 4 N hydrochloric acid ethyl acetate solution 0.7 ml was added and stirred, thereafter produced sedimentation was filtered, and it was washed with ethanol, and thereby 3-hydroxy-4'-methoxy-2-{[4-(4-methyl-1,4-diazepan-1-yl) benzoyl] amino} benzanilide hydrochloride 896 mg was obtained by drying under reduced pressure.

The compounds of Examples 10-16, 42, 51, 52 were synthesised in the same way as in Example 9.

Example 17.

2'-amino-6'-hydroxy-4-(4-methyl-1,4-diazepan-1-yl) benzanilide 2.03 g was dissolved in pyridine 60 ml, and 4-methoxybenzoyl chloride 1.12 g was added at 0 degrees and the mixture was stirred at room temperature for 3 days. The reaction liquor was concentrated under reduced pressure, and chloroform 150 ml was added to the obtained residue, and it was made alkaline using 5 % sodium hydrogen carbonate aqueous solution 150 ml, and it was extracted with chloroform. The obtained organic layer was dried with anhydrous sodium sulphate, thereafter it was concentrated under reduced pressure, toluene was added, and it was concentrated under reduced pressure once again. The obtained residue was purified by silica gel column chromatography with chloroform : methanol : saturated ammonia water (100:10:1) as elution solvent. It was recrystallised from ethanol, and 3-hydroxy-N1-(4-methoxybenzoyl)-N2-[4-(4-methyl-1,4-diazepan-1-yl) benzoyl]-1,2-phenylenediamine 1.74 g was obtained. 3-hydroxy-N1-(4-methoxybenzoyl)-N2-[4-(4-methyl-1,4-diazepan-1-yl) benzoyl]-1,2-phenylenediamine 1.10 g and maleic acid 269 mg were dissolved in 50 % ethanol aqueous solution 11 ml by heating, water 11 ml was added, and it was cooled, and the crystals produced were recovered by filtration, dried, and 3-hydroxy-N1-(4-methoxybenzoyl)-N2-[4-(4-methyl-1,4-diazepan-1-yl) benzoyl]-1,2-phenylenediamine maleate 1.18 g was obtained.

The compounds of Examples 18-35 were synthesised in the same way as in Example 17.

Example 36.

3-hydroxy-N1-(4-methoxybenzoyl)-N2-[4-(4-methyl-1,4-diazepan-1-yl) benzoyl]-1,2-phenylene diamine 500 mg was dissolved in methanol 11 ml, benzyl bromide 215 mg was added at room temperature and the mixture was stirred for five hours. Benzyl bromide 215 mg was added at room temperature, the mixture was stirred for 16 hours, and thereafter the precipitate was recovered by filtration. The obtained precipitate was suspended in N,N-dimethylformamide 11 ml, and bromoacetic acid ethyl ester 210 mg and potassium carbonate 174 mg were added at room temperature and the mixture was stirred at 100 degrees for 30 minutes. The insolubles were filtered, and it was concentrated under reduced pressure. The obtained residue was dissolved in acetic acid 16 ml, and 10 % palladium-carbon powder 100 mg was added, and the mixture was stirred under hydrogen atmosphere of 3 atmosphere, at room temperature for three hours. The reaction liquor was filtered with celite, washed with methanol, next the filtrate was concentrated under reduced pressure. Chloroform 50 ml was added to the obtained residue, and it was made alkaline using 5 % sodium hydrogen carbonate aqueous solution 50 ml, and it was extracted with chloroform. The obtained organic layer was dried with anhydrous sodium sulphate, and thereafter it was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography with chloroform : methanol : saturated ammonia water (100:10:1) as elution solvent, and the crude purified material of ethyl (3-[(4-methoxybenzoyl) amino]-2-{[4-(4-methyl-1,4-diazepan-1-yl) benzoyl] amino} phenoxy) acetate 580 mg was obtained. The crude purified material thereof was refined with ODS column chromatography with 0.001 N hydrochloric acid : methanol (10:4) as elution solvent, and ethyl (3-[(4-methoxybenzoyl) amino]-2-{[4-(4-methyl-1,4-diazepan-1-yl) benzoyl] amino} phenoxy) acetate hydrochloride 350 mg was obtained.

Example 37.

Ethyl (3-[(4-methoxybenzoyl) amino]-2-{[4-(4-methyl-1,4-diazepan-1-yl) benzoyl] amino} phenoxy) acetate hydrochloride 350 mg was dissolved in methanol 6 ml and 1 N aqueous sodium hydroxide 1.8 ml was added at room temperature and the mixture was stirred for two hours. 1 N hydrochloric acid 1.8 ml was added, and it was concentrated under reduced pressure. The obtained residue was refined by ODS column chromatography with 0.001 N hydrochloric acid : acetonitrile (1:1) as elution solvent, and (3-[(4-methoxybenzoyl) amino]-2-{[4-(4-methyl-1,4-diazepan-1-yl) benzoyl] amino} phenoxy) acetic acid hydrochloride 254 mg was obtained.

The compound of Example 38 was synthesised in the same way as in Example 37.

Example 39.

Crude purified material 370 mg of ethyl (3-[(4-methoxybenzoyl) amino]-2-{[4-(4-methyl-1,4-diazepan-1-yl) benzoyl] amino} phenoxy) acetate was dissolved in tetrahydrofuran 7 ml, and sodium tetrahydro borate 108 mg was added at room temperature. A solution of methanol 930 mg dissolved in tetrahydrofuran 7 ml was dropwise added at 60 degrees over a period of 25 minutes. The mixture was stirred at 60 degrees for 2 hours. Water 1 ml was added at room temperature, and it was concentrated under reduced pressure. Aforesaid procedure was carried out with respect to the obtained residue once again, and thereafter the obtained residue was purified by silica gel column chromatography with chloroform : methanol : saturated ammonia water (100:10:1) as elution solvent. The obtained compound was suspended in ethanol 3 ml, and 1 N hydrochloric acid 0.4 ml was added, and it was concentrated under reduced pressure. Acetone 3 ml and distilled water 3 ml were added to the obtained residue, and produced sedimentation was filtered, and 3-(2-hydroxyethoxy)-N1-(4-methoxybenzoyl)-N2-[4-(4-methyl-1,4-diazepan-1-yl) benzoyl]-1,2-phenylenediamine hydrochloride 107 mg was obtained.

Example 40.

3-hydroxy-N1-(4-methoxybenzoyl)-N2-[4-(4H methyl-1,4-diazepan-1-yl) benzoyl]-1,2-phenylene diamine 730 mg was dissolved in tetrahydrofuran 20 ml, and methanol 0.13 ml, triphenyl phosphine 498 mg, diethyl azodicarboxylate 0.23 ml were added and the mixture was stirred at room temperature for 16.5 hours. The reaction liquor was concentrated under vacuum, thereafter the obtained residue was dissolved in chloroform, it was washed with 0.5 N aqueous sodium hydroxide and saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and thereafter concentrated under vacuum. The obtained residue was purified by silica gel column chromatography with chloroform : methanol (95:5 to 93:7) as elution solvent. The obtained crude purified material was dissolved in ethanol 10 ml, 4 N hydrochloric acid ethyl acetate solution 0.4 ml was added, and thereafter it was concentrated under vacuum. The obtained residue was refined by ODS column chromatography with 0.002 N aqueous hydrochloric acid : acetonitrile (97:3 to 85:15), thereafter it was freeze-dried, and 3-methoxy-N1-(4-methoxybenzoyl)-N2-[4-(4-methyl-1,4-diazepan-1-yl) benzoyl]-1,2-phenylenediamine hydrochloride 335 mg was obtained.

Example 41.

3-hydroxy-N1-(4-methoxybenzoyl)-N2-[4-(4-methyl-1,4-diazepan-1-yl) benzoyl]-1,2-phenylene diamine 474 mg was dissolved in N,N-dimethylformamide 15 ml, trimethylamine-sulphur trioxide complex 1.39 g was added and the mixture was stirred at 60 degrees for 79 hours. Furthermore, trimethylamine-sulphur trioxide complex 0.42 g was added, the mixture was stirred at 60 degrees for 38 hours and furthermore, trimethylamine-sulphur trioxide complex 0.42 g was added and the

mixture was stirred at 60 degrees for 23 hours, and thereafter it was concentrated under vacuum. Water was added to the obtained residue, and the mixture was stirred for one hour, thereafter produced sedimentation was recovered by filtration, and it was washed with water. The obtained crude purified material was suspended in ethanol, after stirring, it was filtered, and it was washed with ethanol and water, thereafter it was dried under reduced pressure, and 3-[(4-methoxybenzoyl amino]-2-{[4-(4-methyl-1,4-diazepan-1-yl) benzoyl] amino} phenyl hydrogen sulphate 483 mg was obtained.

Example 43.

N2-[4-(4-benzyl-1,4-diazepan-1-yl) benzoyl]-3-hydroxy-N1-(4-methoxybenzoyl)-1,2-phenylene diamine 11.53 g was dissolved in acetic acid 250 ml, and 10 % palladium-carbon powder 2.5 g was added and, the mixture was stirred under hydrogen atmosphere of 3 atmosphere at room temperature for 44 hours. The reaction liquor was filtered with celite, washed with acetic acid, and next the filtrate was concentrated under vacuum. Toluene was added, it was concentrated under vacuum again, and the residue 11.11 g was obtained. Among the residues, 2.00 g thereof was dissolved in a mixed solvent of chloroform, aqueous sodium hydrogen carbonate, methanol and the mixture was stirred for 12 hours. After separation, the organic layer was washed with saturated aqueous sodium chloride solution, it was dried with anhydrous sodium sulphate and concentrated under vacuum. The obtained residue was suspended in ethanol, it was stirred for three hours, thereafter precipitate was filtered, and it was washed with ethanol. The obtained solid was recrystallised from ethanol, and N2-[4-(1,4-diazepan-1-yl) benzoyl]-3-hydroxy-N1-(4-methoxybenzoyl)-1,2-phenylenediamine was obtained. Furthermore it was crystallised from 0.5 N HCI, and N2-[4-(1,4-diazepan-1-yl) benzoyl]-3-hydroxy-N1-(4-methoxybenzoyl)-1,2-phenylene diamine hydrochloride 878 mg was obtained.

Example 44.

3-hydroxy-N1-(4-methoxybenzoyl)-N2-[4-(1,4-diazepan-1-yl) benzoyl]-1,2-phenylenediamine 857 mg was suspended in dichloromethane 20 ml, and acetic acid 1.2 g and cyclopropane carbaldehyde 261 mg and triacetoxy borohydride 789 mg were added at room temperature. The mixture was stirred for two hours, thereafter cyclopropane carbaldehyde 261 mg and triacetoxy borohydride 789 mg were added at room temperature and furthermore the mixture was stirred for two hours. The reaction liquor was concentrated under reduced pressure, and thereafter chloroform 50 ml was added to the obtained residue, and it was made alkaline using 5 % sodium hydrogen carbonate aqueous solution 50 ml, and it was extracted with chloroform. The obtained organic layer was dried with anhydrous sodium sulphate, and thereafter it was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography with chloroform : methanol : saturated ammonia

water (100:10:1). The obtained compound was suspended in ethanol 13 ml, and 1 N hydrochloric acid 1.9 ml was added, and produced sedimentation was filtered, and 3-hydroxy-N1-(4-methoxybenzoyl)-N2-[4-(4-cyclopropylmethyl-1,4-diazepan-1-yl) benzoyl]-1,2-phenylenediamine hydrochloride 656 mg was obtained.

Example 45.

N2-[4-(1,4-diazepan-1-yl) benzoyl]-3-hydroxy-N1-(4-methoxybenzoyl)-1,2-phenylenediamine 1.3 g was dissolved in ethanol 20 ml, ethyl aceto imidate hydrochloride 1.04 g and triethylamine 1.5 ml were added and the mixture was stirred for 17 hours. Furthermore, ethanol 150 ml, ethyl acetimidate hydrochloride 1.04 g, triethylamine 1.5 ml were added and the mixture was stirred at 50 degrees for 68 hours. The reaction liquor was concentrated under vacuum, and the obtained residue was refined by ODS column chromatography with 0.002 N hydrochloric acid solution : acetonitrile (95:5 to 70:30), thereafter it was freeze-dried, and 3-hydroxy-N2-{4-[4-(1-iminoethyl)-1,4-diazepan-1-yl] benzoyl)-N1-(4-methoxybenzoyl)-1,2-phenylenediamine hydrochloride 515 mg was obtained.

The compounds of Examples 46-48 were synthesised in the same way as in Example 44.

Example 49.

4-(4-methyl-1,4-diazepan-1-yl) benzoic acid hydrochloride 755 mg was dissolved in thionyl chloride 2.2 ml, and the mixture was stirred at 60 degrees for 30 minutes. The reaction liquor was concentrated under reduced pressure, and it was dried to a solid. A solution of 2-amino-5-chloro-N-(5-chloro-2-pyridyl)-3-hydroxybenzamide 891 mg dissolved in pyridine 10 ml was added to the obtained residue, and the mixture was stirred at room temperature for 13 hours. The reaction liquor was concentrated under reduced pressure, thereafter acetic acid 20 ml was added to the obtained residue and the mixture was stirred at room temperature for 17 hours. The reaction liquor was concentrated under reduced pressure, thereafter saturated aqueous sodium bicarbonate solution was added to the obtained residue, it was extracted with chloroform, dried with anhydrous sodium sulphate, and thereafter concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography with chloroform : methanol : ammonia water (97:3:0.3 to 95:5:0.5), and the crude purified material of 5-chloro-N-(5-chloro-2-pyridyl)-3-hydroxy-2-([4-(4-methyl-1,4-diazepan-1-yl) benzoyl] amino} benzamide was obtained. Furthermore, this was refined by ODS column chromatography with acetonitrile : 0.002 N aqueous hydrochloric acid (2:8 to 3:7) as elution solvent, and it was suspended in dilute aqueous hydrochloric acid, freeze-dried, and 5-chloro-N-(5-chloro-2-pyridyl)-3-hydroxy-2-{[4-(4-methyl-1,4-diazepan-1-yl) benzoyl] amino} benzamide hydrochloride 492 mg was obtained.

The compound of Example 50 was synthesised in the same way as in Example 49.

Structural formulae and physico-chemical characteristics of the aforesaid Reference Example compounds and Example compounds are shown in separate Tables 2 and 3. The compounds shown in Tables 4-6 can be easily synthesised by almost the same process of aforesaid Example or the production method, or applying some modifications which are self-evident to a person skilled in the art. Moreover the symbols in the Table have following meanings.

Rf: Reference Example number, Ex: Example number, structure: structural formula, salt: salt, free: free body, DATA: physical properties data, NMR: nuclear magnetic resonance spectrum (TMS internal standard), FAB-MS: mass spectrometry value, Me: methyl, Et: ethyl.

表2

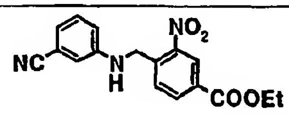
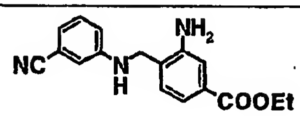
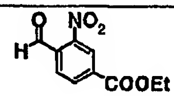
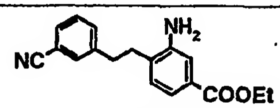
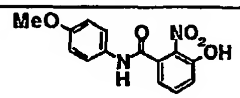
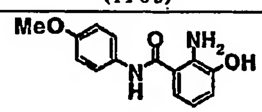
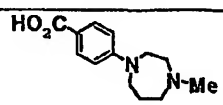
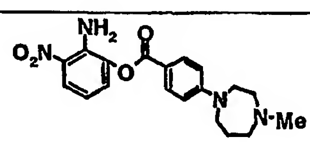
Rf	structure(salt)	DATA
1	 (free)	NMR ($CDCl_3$) : δ :1.42(3H, t, J = 7.2 Hz), 4.43(2H, q, J = 7.2Hz), 4.63(1H, t, J = 5.7 Hz), 4.81(2H, d, J = 6.0 Hz), 6.72 - 6.78(2H, m), 7.01(1H, dt, J = 1.3 Hz, 7.7 Hz), 7.19 - 7.27(1H, m), 7.69(1H, d, J = 8.1 Hz), 8.24(1H, dd, J = 1.7 Hz, 8.0 Hz), 8.73(1H, d, J = 1.7 Hz)
2	 (free)	NMR ($CDCl_3$) : δ :1.39(3H, t, J = 7.1 Hz), 3.96 - 4.16(3H, m), 4.25(2H, d, J = 4.2 Hz), 4.36(2H, q, J = 7.1Hz), 6.85 - 6.93(2H, m), 7.05(1H, dt, J = 1.2 Hz, 7.9 Hz), 7.22(1H, d, J = 7.7 Hz), 7.27(1H, t, J = 8.0 Hz), 7.41(1H, d, J = 1.3 Hz), 7.43(1H, dd, J = 1.7 Hz, 7.7 Hz)
3	 (free)	NMR ($CDCl_3$) : δ : 1.46(3H, t, J=7.2Hz), 4.48(2H, q, J=7.2Hz), 8.00(1H, d, J=8.0Hz), 8.42(1H, d, J=8.0Hz), 8.75(1H, s), 10.46(1H, s)
4	 (free)	NMR ($CDCl_3$) : δ : 1.38(3H, t, J=7.1Hz), 2.82(2H, t, J=8.4Hz), 2.96(2H, t, J=8.4Hz), 4.34(2H, q, J=7.1Hz), 6.97(1H, d, J=8.4Hz), 7.33-7.41(4H, m), 7.44-7.52(2H, m)
5	 (free)	NMR (DMSO-d_6) : δ : 3.74(3H, s), 6.92(2H, d, J = 8.8 Hz), 7.19 - 7.30(2H, m), 7.50(1H, t, J = 8.6 Hz), 7.58(2H, d, J = 9.3 Hz), 10.46(1H, s), 11.25(1H, brs),
6	 (free)	NMR (DMSO-d_6) : δ : 3.74(3H, s), 5.79(2H, s), 6.46(1H, t, J = 7.8 Hz), 6.82(1H, d, J = 7.8 Hz), 6.90(2H, d, J = 8.8 Hz), 7.15(1H, d, J = 7.8 Hz), 7.61(2H, d, J = 8.8 Hz), 9.56(1H, s), 9.81(1H, s),
7	 HCl	NMR (DMSO-d_6) : δ :2.06 - 2.24(1H, m), 2.30 - 2.45(1H, m), 2.77(3H, s), 3.00 - 3.24(2H, m), 3.24 - 3.66(4H, m), 3.70 - 4.00(2H, m), 6.81(2H, d, J = 9.1 Hz), 7.78(2H, d, J = 9.1 Hz), 11.06(1H, s), 12.20(1H, s)
8	 HCl	NMR (DMSO-d_6) δ :2.15 - 2.22(1H, m), 2.34-2.45(1H, m), 2.79(3H, d, J = 5.0Hz), 3.05 - 3.22(2H, m), 3.40 - 3.61(4H, m), 3.79 - 3.88(1H, m), 3.95 - 4.03(1H, m), 6.69 - 6.76(1H, m), 6.93(2H, d, J = 9.0 Hz), 7.05(2H, br), 8.00(2H, d, J = 9.0 Hz), 11.12(1H, br)

表2（続き）

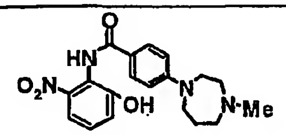
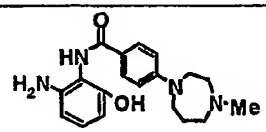
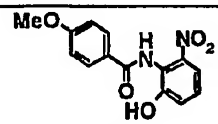
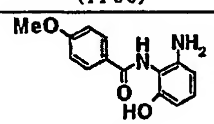
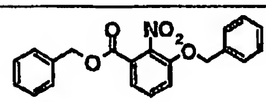
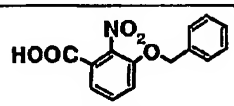
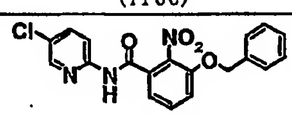
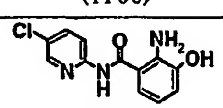
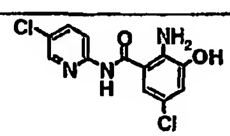
9	 (free)	NMR(DMSO-d_6) δ:1.86-1.95(2H, m), 2.29(3H, s), 2.45 - 2.52(2H, m), 2.65(2H, t, J = 4.4Hz), 3.51(2H, t, J = 6.0 Hz), 3.60(2H, t, J = 4.4 Hz), 6.76(2H, d, J = 9.2 Hz), 7.21-7.28(2H, m), 7.35(1H, dd, J = 6.8Hz, 2.4 Hz), 7.84(2H, d, J = 9.2Hz), 9.53(1H, br)
10	 (free)	NMR(DMSO-d_6): 1.85-1.94(2H, m), 2.26(3H, s), 2.43(2H, t, J=5.6Hz), 2.61(2H, t, J=4.8Hz), 3.51(2H, t, J=6.0Hz), 3.58(2H, t, J=4.8Hz), 4.68(2H, s), 6.16(1H, dd, J=7.6Hz, 1.2Hz), 6.24(1H, dd, J=8.0Hz, 1.2Hz), 6.70-6.81(3H, m), 7.86(1H, d, J=8.8Hz), 8.93(1H, br), 8.94(1H, s)
11	 (free)	NMR(DMSO-d_6): δ:3.88(3H, s), 6.70(1H, dd, J = 7.7 Hz, 8.7 Hz), 7.14(2H, d, J = 8.9 Hz), 7.17 - 7.21(2H, m), 7.43(1H, dd, J = 1.4 Hz, 7.7 Hz), 7.97(1H, dd, J = 1.4 Hz, 8.7 Hz), 8.13(2H, d, J = 8.9 Hz)
12	 (free)	NMR(DMSO-d_6): δ:3.83 - 3.86(2H, m), 3.84(3H, s), 6.68 - 6.72 (1H, m), 6.72 - 6.78(1H, m), 7.06(2H, d, J = 8.7 Hz), 7.06 - 7.12(2H, m), 8.05(2H, d, J = 8.7 Hz), 9.63 - 9.67(1H, br)
13	 (free)	NMR(DMSO-d_6): δ:5.33(4H, s), 7.31 - 7.45 (10H, m), 7.61(1H, dd, J = 1.4 Hz, 7.5 Hz), 7.68(1H, t, J = 7.9 Hz), 7.74(1H, dd, J = 1.5 Hz, 8.2 Hz)
14	 (free)	NMR(DMSO-d_6): δ:5.32(2H, s), 7.31 - 7.44 (5H, m), 7.56(1H, dd, J = 1.7 Hz, 7.3 Hz), 7.64(1H, t, J = 7.9 Hz), 7.68(1H, dd, J = 1.7 Hz, 8.3 Hz)
15	 (free)	NMR($CDCl_3$): δ:5.23(2H, s), 7.22 - 7.26 (2H, m), 7.31 - 7.39 (5H, m), 7.46(1H, t, J = 8.3 Hz), 7.69(1H, dd, J = 2.7 Hz, 9.1 Hz), 8.03(1H, d, J = 2.9 Hz), 8.26(1H, d, J = 8.8 Hz), 9.01(1H, brs)
16	 (free)	NMR(DMSO-d_6): δ:5.93(2H, s), 6.44(1H, t, J = 7.9Hz), 6.82(1H, d, J = 7.7 Hz), 7.27(1H, d, J = 7.3 Hz), 7.93(1H, dd, J = 2.6 Hz, 9.0 Hz), 8.14(1H, d, J = 8.8 Hz), 8.41(1H, d, J = 2.4 Hz), 9.60(1H, s), 10.46(1H, s)
17	 (free)	NMR(DMSO-d_6): δ:6.04(2H, brs), 6.80(1H, d, J = 2.4 Hz), 7.36(1H, d, J = 2.0 Hz), 7.93(1H, dd, J = 2.5 Hz, 8.8 Hz), 8.11(1H, d, J = 9.3 Hz), 8.42(1H, d, J = 2.5 Hz), 10.16(1H, brs), 10.67(1H, s)

表2（続き）

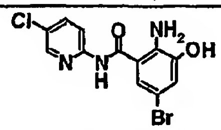
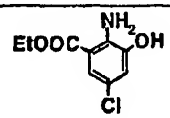
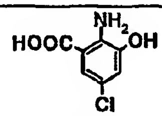
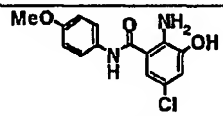
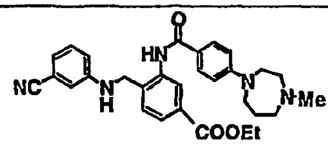
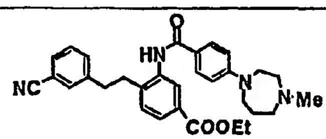
18	 (free)	NMR(DMSO-d_6): δ:6.06(2H, brs), 6.90(1H, d, J = 2.2 Hz), 7.47(1H, d, J = 2.2 Hz), 7.93(1H, dd, J = 2.8 Hz, 9.0 Hz), 8.10(1H, d, J = 9.0 Hz), 8.42(1H, d, J = 2.2 Hz), 10.15(1H, brs), 10.69(1H, s)
19	 (free)	NMR($CDCl_3$): δ:1.38(3H, t, J = 7.3 Hz), 4.33(2H, q, J = 7.3 Hz), 6.00 - 6.30(3H br), 6.81(1H, d, J = 2.0 Hz), 7.48(1H, d, J = 2.4 Hz)
20	 (free)	NMR(DMSO-d_6): δ:3.37(1.5H, brs), 6.78(1H, d, J = 2.4 Hz), 7.17(1H, d, J = 2.5 Hz), 8.34(1.5H, brs), 10.19(1H, s)
21	 (free)	NMR(DMSO-d_6): δ:3.74(3H, s), 5.93(2H, brs), 6.78(1H, d, J = 1.9 Hz), 6.91(2H, d, J = 9.3 Hz), 7.23(1H, d, J = 2.5 Hz), 7.59(2H, d, J = 9.3 Hz), 9.90(1H, s), 10.09(1H, brs)
22	 (free)	NMR($CDCl_3$): δ:1.39(3H, t, J = 7.4 Hz), 1.97 - 2.06(2H, m), 2.38(3H, s), 2.53 - 2.59(2H, m), 2.68 - 2.73(2H, m), 3.51(2H, t, J = 6.4 Hz), 3.57 - 3.63(2H, m), 4.34 - 4.42(5H, m), 6.58(2H, d, J = 8.8 Hz), 6.96 - 7.01(2H, m), 7.12(1H, d, J = 7.8 Hz), 7.31(1H, t, J = 7.8 Hz), 7.40(1H, d, J = 8.3 Hz), 7.65 (2H, d, J = 8.7 Hz), 7.81(1H, dd, J = 1.5 Hz, 7.8 Hz), 8.67(1H, d, J = 2.0 Hz), 8.85(1H, s), FAB-MS(m/z): 512$(M+H)^+$
23	 (free)	NMR($CDCl_3$): δ: 1.37(3H, t, J=7.1Hz), 2.43-2.54(2H, br), 2.76(3H, s), 2.93-3.01(4H, m), 3.14-3.22(2H, br), 3.23-3.29(2H, br), 3.59(2H, t, J=6.4Hz), 3.89-3.95(2H, m), 4.33(2H, q, J=7.1Hz), 6.72(2H, d, J=8.9Hz), 7.20(1H, d, J=7.3Hz), 7.27-7.35(3H, m), 7.41(1H, d, J=7.3Hz), 7.68-7.73(1H, m), 7.75(2H, d, J=8.3Hz), 7.85(1H, dd, J=1.8Hz, 8.3Hz), 8.23(1H, s) FAB-MS(m/z): 511 $(M+H)^+$

表3

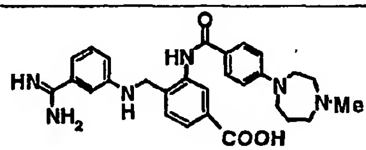
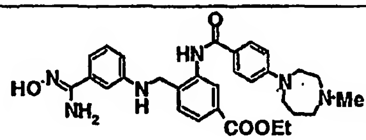
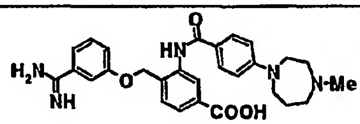
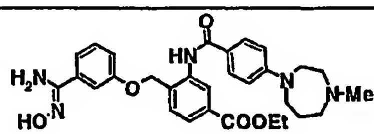
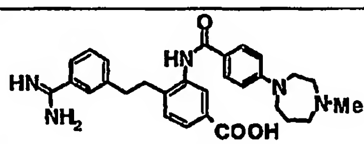
Ex	structure (salt)	DATA
1	 HCl	NMR (DMSO-d_6) : δ : 2.16-2.26 (2H, br), 2.67 (3H, s), 2.95 - 3.49 (5H, br), 3.54 (2H, t, J = 6.3 Hz), 3.73- 3.86 (2H, br), 4.44 (2H, d, J = 5.3 Hz), 6.79 - 6.87 (4H, m), 6.94 (1H, d, J = 7.3 Hz), 6.98 (1H, s), 7.26 (1H, t, J = 8.3 Hz), 7.44 (1H, d, J = 7.8 Hz), 7.75 (1H, dd, J = 2.0 Hz, 7.8 Hz), 7.94 (2H, d, J = 9.2 Hz), 7.98 (1H, d, J = 1.9 Hz), 9.07 (2H, s), 9.22 (2H, s), 9.98 (2H, s) FAB-MS (m/z) : 501 $(M+H)^+$
2	 HCl	NMR (DMSO-d_6) : δ : 1.31 (3H, t, J = 7.3 Hz), 2.79 (3H, d, J = 4.4 Hz), 4.31 (2H, q, J = 7.3 Hz), 4.43 (2H, s), 6.76 - 6.91 (6H, m), 7.26 (1H, t, J = 8.4 Hz), 7.46 (1H, d, J = 8.3 Hz), 7.77 (1H, dd, J = 8.3, 1.4 Hz), 7.96 (2H, d, J = 8.8 Hz), 8.01 (1H, d, J = 1.4 Hz), FAB-MS (m/z) : 545 $(M+H)^+$
3	 HCl	NMR (DMSO-d_6) : δ : 2.02 - 2.09 (2H, m), 2.76 - 2.84 (2H, m), 2.87 - 2.98 (2H, m), 3.32 (3H, br s), 3.51 - 3.65 (2H, m), 3.68 - 3.73 (2H, m), 5.31 (2H, s), 6.81 (2H, d, J = 8.8 Hz), 7.31 (1H, dd, J = 2.4 Hz , 8.4 Hz), 7.40 (1H, d, J = 8.0 Hz), 7.46 - 7.49 (1H, m), 7.50 - 7.54 (1H, m), 7.62 (1H, d, J = 8.4 Hz), 7.82 (1H, dd, J = 2.0 Hz , 8.0 Hz), 7.89 (2H, d, J = 8.8 Hz), 8.03 (1H, d, J = 1.6 Hz), 9.33 (4H, br s), 9.90 (1H, s) FAB-MS (m/z) : 502 $(M+H)^+$
4	 HCl	NMR (DMSO-d_6) : δ : 1.33 (3H, t, J = 7.4 Hz), 2.79 (3H, s), 4.32 (2H, q, J = 7.3 Hz), 5.26 (2H, s), 6.86 (2H, d, J = 8.8 Hz), 7.03 - 7.08 (1H, m), 7.26 - 7.37 (3H, m), 7.67 (1H, d, J = 8.4 Hz), 7.84 (1H, dd, J = 1.6 Hz , 8.4 Hz), 7.91 (2H, d, J = 8.8 Hz), 8.10 (1H, d, J = 1.6 Hz), FAB-MS (m/z) : 546 $(M+H)^+$
5	 HCl	NMR (DMSO-d_6) : δ : 2.12-2.24 (1H, m), 2.38-2.49 (1H, m), 2.79 (3H, d, J=4.9Hz), 3.92-3.99 (2H, m), 3.01-3.20 (4H, m), 3.39-3.58 (4H, m), 3.76-3.86 (1H, m), 3.90-4.03 (1H, m), 6.86 (2H, d, J=9.3Hz), 7.41 (1H, d, J=8.3Hz), 7.43-7.49 (2H, m), 7.61-7.67 (1H, m), 7.75 (2H, dd, J=1.5Hz, 9.3Hz), 7.88 (1H, d, J=1.5Hz), 7.98 (2H, d, J=9.3Hz), 9.35 (2H, s), 9.45 (2H, s), 9.91 (1H, s), 11.37 (1H, s) FAB-MS (m/z) : 500 $(M+H)^+$

表3（続き）

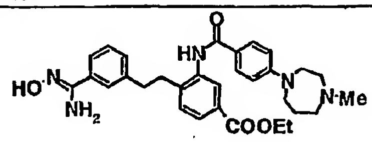
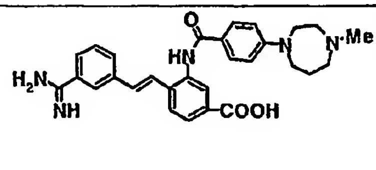
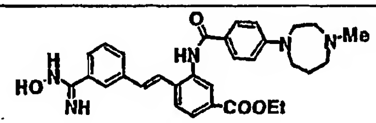
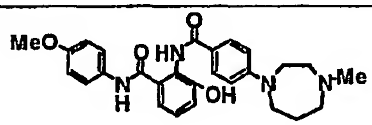
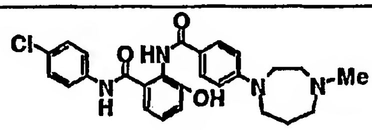
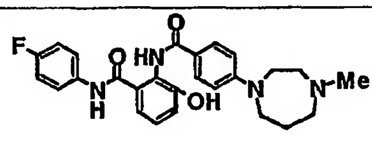
6	 HCl	NMR (DMSO-d_6) : δ : 1.32 (3H, t, J=7.0Hz), 2.78 (3H, s), 4.31 (2H, q, J=7.0Hz), 6.86 (2H, d, J=8.8Hz), 7.40-7.46 (3H, m), 7.53 (1H, dt, J=1.9Hz, 7.1Hz), 7.62 (1H, s), 7.76 (1H, dd, J=1.9Hz, 7.1Hz), 7.90 (1H, d, J=1.4Hz), 7.96 (2H, d, J=8.8Hz) FAB-MS (m/z) : 544 (M+H)$^+$
7	 HCl	NMR (DMSO-d_6) : δ : 2.79 (3H, d, J = 4.8 Hz), 6.87 (2H, d, J = 8.8 Hz), 7.43 (1H, d, J = 16.0 Hz), 7.53 (1H, d, J = 16.0 Hz), 7.60 - 7.64 (1H, m), 7.73 (1H, d, J = 8.0 Hz), 7.83 (1H, dd, J = 1.6 Hz, 8.4 Hz), 7.89 (1H, d, J = 7.6 Hz), FAB-MS (m/z) : 498 (M+H)$^+$
8	 HCl	NMR (DMSO-d_6) : δ : 1.33 (3H, t, J = 7.2 Hz), 2.80 (3H, d, J = 4.8 Hz), 4.34 (2H, q, J = 7.2 Hz), 6.88 (2H, d, J = 9.2 Hz), 7.42 - 7.51 (2H, m), 7.58 - 7.65 (2H, m), 7.84 - 7.87 (2H, m), 7.90 (1H, s), 7.96 - 8.01 (4H, m) FAB-MS (m/z) : 542 (M+H)$^+$
9	 HCl	NMR (DMSO-d_6) : δ : 2.10 - 2.41 (2H, m), 2.78 (3H, s), 3.02 - 3.22 (2H, m), 3.35 - 3.57 (4H, m), 3.67 - 3.81 (4H, m), 3.87 - 3.99 (1H, m), 6.80 - 6.95 (4H, m), 7.11 (1H, d, J = 7.3 Hz), 7.17 - 7.28 (2H, m), 7.57 (2H, d, J = 8.8 Hz), 7.85 (2H, d, J = 8.8 Hz), 10.02 (1H, s), 10.19 (1H, s), 10.41 (1H, s), 10.64 (1H, brs) FAB-MS (m/z) : 475 (M+H)$^+$
10	 HCl	NMR (DMSO-d_6) : δ : 2.78 (3H, s), 6.84 (2H, d, J = 9.3 Hz), 7.10 - 7.13 (1H, m), 7.15 - 7.18 (1H, m), 7.22 - 7.26 (1H, m), 7.36 (2H, d, J = 8.8 Hz), 7.71 (2H, d, J = 8.7 Hz), 7.85 (2H, d, J = 8.8 Hz) FAB-MS (m/z) : 479 (M+H)$^+$
11	 HCl	NMR (DMSO-d_6) : δ : 2.10 - 2.22 (1H, m), 2.28 - 2.41 (1H, m), 2.77 (3H, d, J = 4.9 Hz), 3.02 - 3.21 (2H, m), 3.38 - 3.57 (4H, m), 3.75 (1H, dd, J = 9.7 Hz, 16.1 Hz), 3.93 (1H, dd, J = 2.9 Hz, 16.6 Hz), 6.85 (2H, d, J = 8.8 Hz), 7.09 - 7.27 (5H, m), 7.69 (2H, dd, J = 5.1 Hz, 9.1 Hz), 7.85 (2H, d, J = 8.8 Hz), 9.75 - 10.10 (1H, br), 10.14 (1H, s), 10.36 (1H, s), 10.86 (1H, brs) FAB-MS (m/z) : 463 (M+H)$^+$

表3（続き）

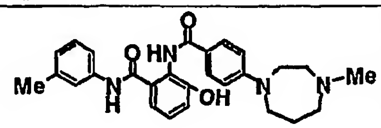
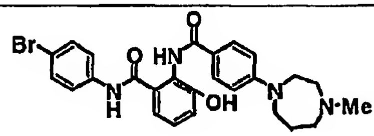
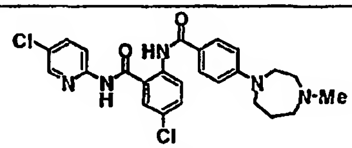
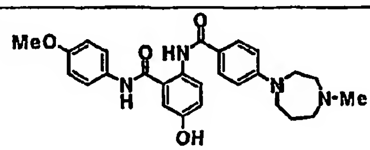
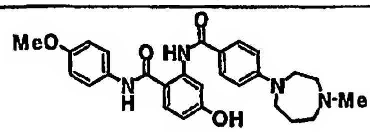
12	 HCl	NMR(DMSO-d_6): δ:2.11 - 2.40(2H, m), 2.27(3H, s), 2.78(3H, s), 3.01 - 3.22(2H, m), 3.38 - 3.55(4H, m), 3.73(1H, dd, J = 9.7 Hz, 16.1 Hz), 3.93(1H, d, J = 15.1 Hz), 6.83 - 6.91(3H, m), 7.11(1H, dd, J = 1.4 Hz, 8.3 Hz), 7.16 - 7.20(2H, m), 7.24 (1H, t, J = 7.8 Hz), 7.44(1H, d, J = 8.3 Hz), 7.49(1H, s), 7.86(2H, d, J = 8.8 Hz), 9.96(1H, s), 10.14(1H, s), 10.17(1H, s), 10.54(1H, brs) FAB-MS(m/z): 459(M+H)$^+$
13	 HCl	NMR(DMSO-d_6): δ:2.79(3H, d, J = 2.4 Hz), 6.84(2H, d, J = 9.3 Hz), 7.11(1H, dd, J = 1.3 Hz, 8.1 Hz), 7.16(1H, d. J = 6.8 Hz), 7.24 (1H, t, J = 7.8 Hz), 7.48(2H, d, J = 8.8 Hz), 7.65(2H, d, J = 8.8 Hz), 7.84(2H, d, J = 8.8 Hz), 9.95(1H, s), 9.97(1H, s), 10.39(1H, s), 10.48 - 10.65(1H, br) FAB-MS(m/z): 523(M+H)$^+$
14	 HCl	NMR(DMSO-d_6): δ:2.12 - 2.20(1H, m), 2.32 - 2.43(1H, m), 2.78(3H, d, J = 4.8 Hz), 3.05 - 3.20(2H, m), 3.39 - 3.56(4H, m), 3.73 - 3.82(1H, m), 3.91 - 3.97(1H, m), 6.90(2H, d, J = 8.7 Hz), 7.65(1H, dd, J = 2.4 Hz , 8.8 Hz), 7.79(2H, d, J = 8.8 Hz), 7.99 - 8.02(2H, m), 8.11 (1H, d, J = 8.8 Hz), 8.43(1H, d, J = 8.8 Hz), 8.48(1H, d, J = 2.5 Hz), 10.94(1H, br s), 11.23(1H, s), 11.29(1H, s) FAB-MS(m/z): 498(M)$^+$
15	 (free)	NMR(DMSO-d_6): δ:2.25(3H, s), 3.75(3H, s), 6.79(2H, d, J = 8.8 Hz), 6.91 - 7.01(3H, m), 7.24(1H, d, J = 2.5 Hz), 7.61(2H, d: J = 8.8 Hz), 7.69 (2H, d, J = 8.8 Hz), 8.28(1H, d, J = 8.8 Hz), FAB-MS(m/z): 475(M+H)$^+$
16	 (free)	NMR(DMSO-d_6): δ:2.25 (3H, s), 3.76 (3H, s), 6.55 (1H, dd, J = 8.8, 2.4 Hz), 6.82 (2H, d, J = 9.3 Hz), 6.95 (2H, d, J = 8.8 Hz), 7.57 (2H, d, J = 8.8 Hz), 7.74 (2H, d, J = 9.3Hz), 7.84 (1H, d, J = 8.8 Hz), 8.27 (1H, d, J = 2.4 Hz), FAB-MS(m/z): 475 (M+H)$^+$

表３（続き）

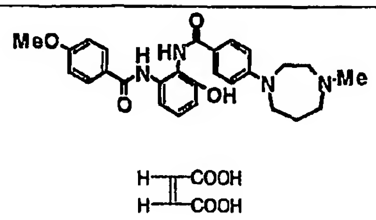
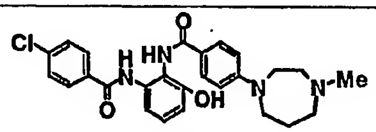
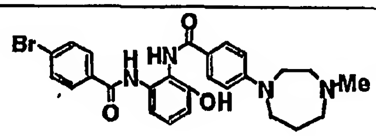
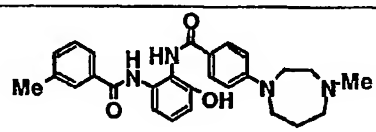
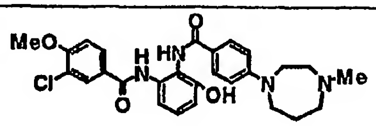
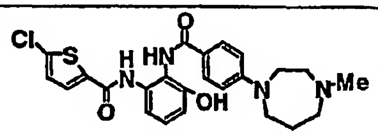
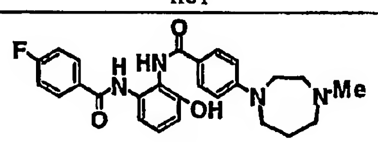
17		NMR (DMSO-d_6) : δ :2.11 - 2.20 (2H, m), 2.83 (3H, s), 3.20 - 3.45 (4H, m), 3.52 (2H, t, J = 6.0 Hz), 3.72 - 3.88 (5H, m), 6.03 (2H, s), 6.80 (1H, d, J = 8.0 Hz), 6.85 (2H, d, J = 8.8 Hz), 7.04 (2H, d, J = 8.8 Hz), 7.14 (1H, t, J = 8.0 Hz), 7.24 (1H, d, J = 8.0 Hz), 7.85 (2H, d, J = 8.8 Hz), 7.91 (2H, d, J = 8.8 Hz), 9.47 (1H, s), 9.67 (1H, s), 9.77 (1H, s) FAB-MS (m/z) : 475 (M+H)$^+$
18	 HCl	NMR (DMSO-d_6) : δ :2.79 (3H, s), 6.82 - 6.86 (3H, m), 7.13 - 7.17 (1H, m), 7.22 (1H, d, J = 8.3 Hz), 7.58 (2H, d, J = 8.3 Hz), 7.89 - 7.93 (4H, m), FAB-MS (m/z) : 479 (M+H)$^+$
19	 HCl	NMR (DMSO-d_6) : δ :2.79 (3H, s), 6.82 - 6.86 (3H, m), 7.13 - 7.17 (1H, m), 7.22 (1H, d, J = 7.8 Hz), 7.72 (2H, d, J = 8.3 Hz), 7.83 (2H, d, J = 8.3 Hz), 7.92 (2H, d, J = 8.8 Hz) FAB-MS (m/z) : 523 , 525 (M+H)$^+$
20	 HCl	NMR (DMSO-d_6) : δ :2.79 (3H, s), 6.82 (1H, d, J = 8.3 Hz), 6.86 (2H, d, J = 8.8 Hz), 7.13 - 7.17 (1H, m), 7.27 (1H, d, J = 8.4 Hz), 7.36 - 7.79 (2H, m), 7.64 - 7.68 (2H, m), 7.95 (2H, d, J = 8.3 Hz), 9.56 (1H, s) FAB-MS (m/z) : 459 (M+H)$^+$
21	 HCl	NMR (DMSO-d_6) : δ : 2.69 (3H, s), 3.92 (3H, s), 6.81 - 6.84 (3H, m), 7.14 (1H, dd, J = 7.8, 8.3Hz), 7.22 (1H, d, J = 7.8Hz), 7.27 (1H, d, J = 8.8Hz), 7.88 (1H, dd, J = 2.0, 8.3Hz), 7.93 (2H, d, J = 8.8)), 7.95 (1H, d, J = 2.0Hz) FAB-MS m/z: 609 (M$^+$)
22	 HCl	NMR (DMSO-d_6) : δ :2.80 (3H, d, J =3.9 Hz), 6.79 - 6.88 (3H, m), 7.10 - 7.18 (2H, m), 7.24 (1H, d, J = 3.9Hz), 7.72 (1H, d, J = 3.9Hz), 7.95 (2H, d, J = 8.8Hz), FAB-MS m/z: 485 (M$^+$)
23	 HCl	NMR (DMSO-d_6) : δ :2.78 (3H, s), 6.82 - 6.85 (3H, m), 7.13 - 7.17 (1H, m), 7.22 (1H, d, J = 7.8 Hz), 7.32 - 7.37 (2H, m), 7.93 (2H, d, J = 8.8 Hz), 7.95 - 7.99 (2H, m) FAB-MS (m/z) : 463 (M+H)$^+$

表3（続き）

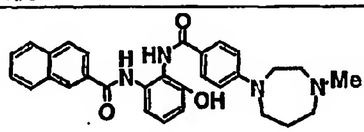
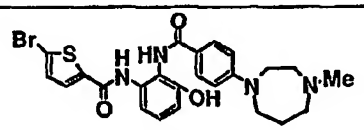
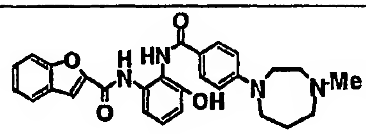
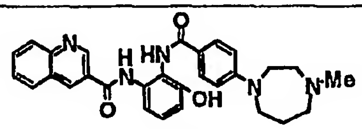
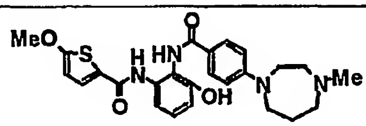
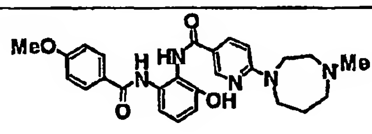
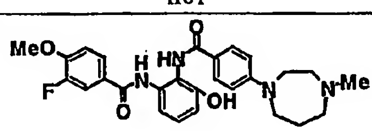
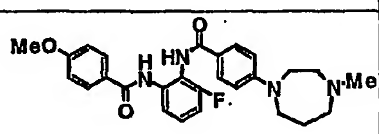
24	 HCl	NMR (DMSO-d_6) : δ :2.76 (3H, s), 6.83 − 6.87 (3H, m), 7.16 − 7.20 (1H, m), 7.31 (1H, d, J = 8.3 Hz), 7.59 − 7.66 (2H, m), 7.94 − 8.04 (6H, m), 8.50 (1H, s), FAB-MS (m/z) : 495 (M+H)$^+$
25	 HCl	NMR (DMSO-d_6) : δ :2.80 (3H, d, J =4.3 Hz), 6.81 − 6.86 (3H, m), 7.11 − 7.17 (2H, m), 7.33 (1H, d, J = 3.9Hz), 7.66 (1H, d, J = 4.4Hz), 7.94 (2H, d, J = 8.8Hz) FAB-MS (m/z) : 529, 531 (M+H)$^+$
26	 HCl	NMR (DMSO-d_6) : δ :2.75 (3H, s), 6.84 − 6.88 (3H, m), 7.15 − 7.19 (1H, m), 7.33 − 7.37 (2H, m), 7.47 − 7.51 (1H, m), 7.57 (1H, d, J = 8.3 Hz), 7.67 (1H, s), 7.80 (1H, d, J = 7.8 Hz), 8.00 (2H, d, J = 8.3 Hz) FAB-MS (m/z) : 485 (M+H)$^+$
27	 HCl	NMR (DMSO-d_6) : δ : 2.75 (3H, d, J = 4.9 Hz), 6.83 (2H, d, J = 9.3 Hz), 6.88 (1H, d, J = 7.8Hz), 7.17 − 7.21 (1H, m), 7.29 (1H, d, J = 7.8 Hz), 7.79 − 7.82 (1H, m), 7.98 − 8.01 (3H, m), 8.17 − 8.20 (2H, m), 9.16 (1H, s), 9.44 (1H, d, J = 1.9 Hz) FAB-MS (m/z) : 496 (M+H)$^+$
28	 HCl	NMR (DMSO-d_6) : δ :2.80 (3H, d, J = 2.4 Hz), 6.40 (1H, d, J = 3.9 Hz), 6.80 (1H, dd, J = 1.6Hz, 7.8Hz), 6.86 (2H, d, J = 8.8 Hz), 7.10 − 7.18 (2H, m), 7.53 (1H, d, J = 3.9 Hz), 7.94 (2H, d, J = 8.8Hz) FAB-MS (m/z) : 481 (M+H)$^+$
29	 HCl	NMR (DMSO-d_6) : δ :2.79 (3H, d, J = 5.9 Hz), 3.81 (3H, s), 6.80 (1H, d, J = 8.3 Hz), 6.85 (1H, d, J = 8.8 Hz), 7.03 (2H, d, J = 8.8 Hz), 7.12 − 7.17 (1H, m), 7.24− 7.27 (1H, m), 7.86 (2H, d, J = 8.8 Hz), 8.18 (1H, d, J = 8.7 Hz), 8.79 (1H, s) FAB-MS (m/z) : 476 (M+H)$^+$
30	 HCl	NMR (DMSO-d_6) : δ :2.79 (3H, s), 6.82 − 6.86 (3H, m), 7.12 − 7.16 (1H, m), 7.22 (1H, d, J = 7.8 Hz), 7.27 − 7.31 (1H, m), 7.72 − 7.77 (2H, m), 7.94 (2H, d, J = 8.3 Hz), FAB-MS (m/z) : 493 (M+H)$^+$
31	 HCl	NMR (DMSO-d_6) : δ :2.79 (3H, d, J = 5.9 Hz), 3.05 − 3.21 (2H, m), 3.82 (3H, s), 6.85 (2H, d, J = 9.3 Hz), 7.03 (2H, d, J = 8.8 Hz), 7.13 − 7.18 (1H, m), 7.31 − 7.37 (1H, m), 7.55 − 7.59 (1H, m), 7.89 (2H, d, J = 8.8 Hz), 7.94 (2H, d, J = 8.7 Hz) FAB-MS (m/z) : 477 (M+H)$^+$

表3（続き）

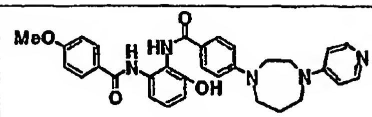
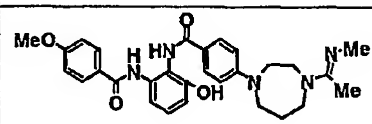
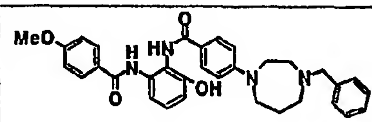
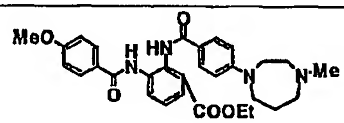
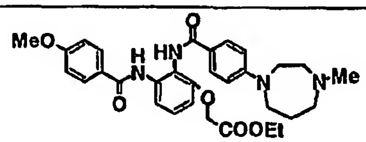
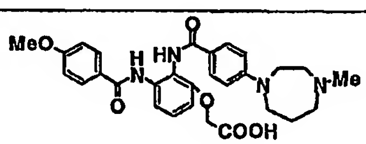
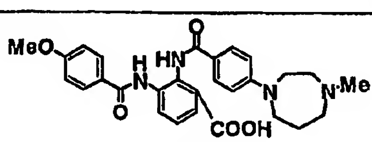
32	 HCl	NMR (DMSO-d_6) : δ : 1.82 – 2.01 (2H, m), 3.46 – 3.89 (11H, m), 6.80 (1H, d, J = 7.8 Hz), 6.86 (2H, d, J = 8.8 Hz), 6.97 – 7.21 (5H, m), 7.25 (1H, d, J = 8.3 Hz), 7.78 – 7.94 (4H, m), 8.18 (2H, s), 9.51 (1H, s), 9.66 (1H, brs), 9.82 (1H, s), 13.46 (1H, brs), FAB-MS (m/z) : 538 $(M+H)^+$
33	 HCl	NMR (DMSO-d_6) : δ : 2.24 (1.5H, s), 2.26 (1.5H, s), 2.84 – 2.95 (3H, m), 6.81 (1H, d, J = 7.8 Hz), 6.84 – 6.93 (2H, m), 7.04 (2H, d, J = 8.8 Hz), 7.14 (1H, t, J = 8.3 Hz), 7.24 (1H, d, J = 8.3 Hz), 7.87 (2H, d, J = 8.8 Hz), 7.91 (2H, d, J = 8.9 Hz) FAB-MS (m/z) : 516 $(M+H)^+$
34	 HCl	NMR (DMSO-d_6) : δ : 6.80 (1H, dd, J = 0.9 Hz, 8.3 Hz), 6.85 (2H, d, J = 8.7 Hz), 7.03 (2H, d, J = 8.7 Hz), 7.14 (1H, t, J = 8.3 Hz), 7.24 (1H, d, J = 7.8 Hz), 7.43 – 7.51 (3H, m), 7.54 – 7.61 (2H, m), 7.86 (2H, d, J = 8.7 Hz), 7.91 (2H, d, J = 8.7 Hz) FAB-MS (m/z) : 551 $(M+H)^+$
35	 HCl	NMR (DMSO-d_6) : δ : 1.14 (3H, t, J = 6.8 Hz), 2.80 (3H, d, J = 4.4 Hz), 3.83 (3H, s), 4.16 (2H, q, J = 7.2 Hz), 6.86 (2H, d, J = 8.8 Hz), 7.06 (2H, d, J = 8.8 Hz), 7.39 – 7.43 (1H, m), 7.68 (1H, dd, J = 1.5 Hz , 7.8 Hz), 7.86 – 7.88 (3H, m), 7.94 (2H, d, J = 8.7 Hz) FAB-MS (m/z) : 531 $(M+H)^+$
36	 HCl	NMR (DMSO-d_6) : δ : 1.21 (3H, t, J =7.3 Hz), 2.78 (3H, d, J = 4.9 Hz), 4.17 (2H, q, J = 7.3 Hz), 4.83 (2H, s), 6.86 (2H, d, J = 9.3 Hz), 6.92 (1H, d, J = 7.3 Hz), 7.04 (2H, d, J = 8.8 Hz), 7.25 – 7.29 (1H, m), 7.49 (1H, d, J = 7.8 Hz), 7.86 (2H, d, J = 8.8 Hz), 7.93 (2H, d, J = 8.8 Hz) FAB-MS (m/z) : 561 $(M+H)^+$
37	 HCl	NMR (DMSO-d_6) : δ : 2.78 (3H, s), 4.75 (2H, s), 6.86 (2H, d, J = 9.3 Hz), 6.94 (1H, d, J = 7.3 Hz), 7.04 (2H, d, J = 8.8 Hz), 7.26 – 7.30 (1H, m), 7.50 (1H, d, J = 7.9 Hz), 7.85 (2H, d, J = 8.8 Hz), 7.95 (2H, d, J = 8.8 Hz) FAB-MS (m/z) : 533 $(M+H)^+$
38	 HCl	NMR (DMSO-d_6) : δ : 2.77 (3H, d, J = 4.4 Hz), 6.87 (2H, d, J = 8.7 Hz), 7.05 (2H, d, J = 8.8 Hz), 7.38 – 7.42 (1H, m), 7.75 (1H, d, J = 7.3 Hz), 7.88 – 7.94 (6H, m) FAB-MS (m/z) : 503 $(M+H)^+$

表3（続き）

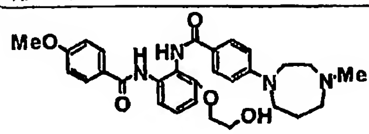
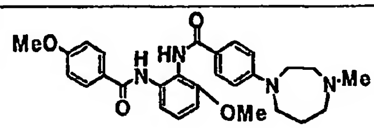
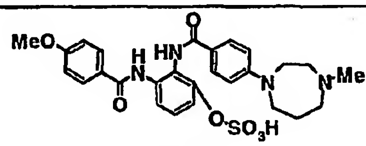
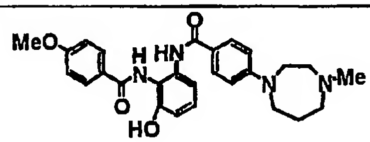
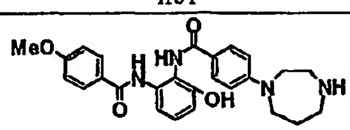
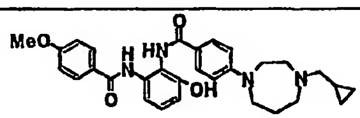
39	 HCl	NMR (DMSO-d_6) : δ : 2.12 - 2.22(1H, m), 2.26 - 2.39(1H, m), 2.79(3H, d, J = 3.9 Hz), 3.05 - 3.21(2H, m), 3.39 - 3.55(4H, m), 3.66 - 3.79(3H, m), 3.81(3H, s), 3.90 - 3.97(1H, m), 4.11(2H, t, J = 4.9 Hz), 4.86(1H, br s), 6.86(2H, d, J = 8.8 Hz), 6.97(1H, d, J = 7.4 Hz), 7.04(2H, d, J = 8.8 Hz), 7.25 - 7.29(1H, m), 7.42(1H, d, J = 8.3 Hz), 7.86(2H, d, J = 8.7 Hz), 7.92(2H, d, J = 8.8 Hz), 9.55(1H, s), 9.89(1H, s), 10.67(1H, br s) FAB-MS (m/z) : 519 $(M+H)^+$
40	 HCl	NMR (DMSO-d_6) : δ : 2.79(3H, d, J = 4.9 Hz), 6.85(2H, d, J = 8.8 Hz), 6.95(1H, d, J = 8.3 Hz), 7.02(2H, d, J = 8.7 Hz), 7.29(1H, t, J = 8.3 Hz), 7.42(1H, d, J = 8.3 Hz), 7.84(2H, d, J = 8.8 Hz), 7.92(2H, d, J = 8.8 Hz) FAB-MS (m/z) : 489 $(M+H)^+$
41	 (free)	NMR (DMSO-d_6) : δ :2.08 - 2.23(2H, m), 2.84(3H, s), 3.10 - 4.05(11H, m), 6.93(2H, d, J = 9.3 Hz), 6.95(1H, d, 8.3 Hz), 7.01-7.08(3H, m), 7.28(1H, t, J = 8.3 Hz), 7.7(1H, dd, J = 1.4 Hz, 8.3 Hz), 7.83(2H, d, J = 8.8 Hz), 7.92(2H, d, J = 9.2Hz), 9.4(1H, brs), 9.91(1H, s), 10.37(1H, s) FAB-MS (m/z) : 553 $(M-H)^+$
42	 HCl	NMR (DMSO-d_6) : δ :2.79(3H, d = 4.9 Hz), 6.78(1H, d, J = 7.8 Hz), 6.82(2H, d, J = 8.8 Hz), 7.06(2H, d, J = 8.8 Hz), 7.13(1H, t, J = 7.8 Hz), 7.30(1H, d, J = 7.8 Hz), 7.75(2H, d, J = 8.8 Hz), 8.01(2H, d, J = 8.8 Hz), FAB-MS (m/z) : 475 $(M+H)^+$
43	 HCl	NMR (DMSO-d_6) : δ : 6.81(1H, dd, J = 1.5, 8.3 Hz), 6.86(2H, d, J = 8.8 Hz), 7.03(2H, d, J = 8.7 Hz), 7.13(1H, t, J = 8.3 Hz), 7.25(1H, d, J = 8.3 Hz), 7.87(2H, d, J = 8.8 Hz), 7.93(2H, d, J = 8.8 Hz), FAB-MS (m/z) : 461 $(M+H)^+$
44	 HCl	NMR (DMSO-d_6) : δ : 0.35 - 0.43(2H, m), 0.61 - 0.67(2H, m), 1.08 - 1.15(1H, m)6.81(1H, dd, J = 1.0 Hz , 8.8 Hz), 6.86(2H, d, J = 8.8 Hz), 7.03(2H, d, J = 8.3 Hz), 7.11 - 7.16(1H, m), 7.24(1H, dd, J = 1.0 Hz , 7.9 Hz), 7.87(2H, d, J = 8.8 Hz), 7.93(2H, d, J = 8.8 Hz), FAB-MS (m/z) : 515 $(M+H)^+$

表3（続き）

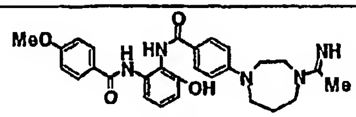
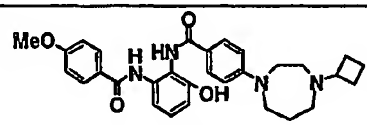
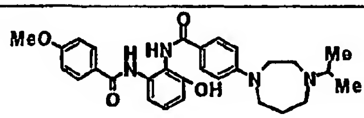
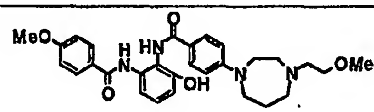
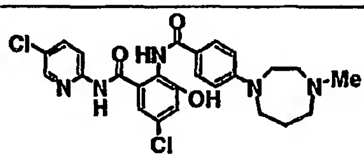
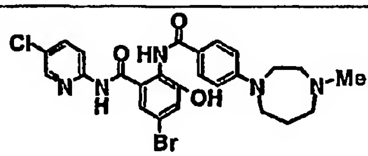
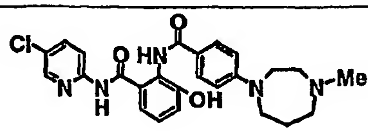
45	 HCl	NMR(DMSO-d_6): δ:6.81(1H, d, J = 8.3 Hz), 6.84 - 6.93(2H, m), 7.03(2H, d, J = 9.3 Hz), 7.13(1H, t, J = 8.3 Hz), 7.25(1H, d, J = 8.3 Hz), 7.88(2H, d, J = 8.2 Hz), 7.92(2H, d, J = 8.3 Hz) FAB-MS(m/z): 502(M+H)$^+$
46	 HCl	NMR(DMSO-d_6): δ: 6.80 - 6.86(3H, m), 7.03(2H, d, J = 8.8 Hz), 7.11 - 7.16(1H, m), 7.24(1H, dd, J = 1.0 Hz, 7.8 Hz), 7.87(2H, d, J = 8.8 Hz), 7.93(2H, d, J = 8.8 Hz) FAB-MS(m/z): 515(M+H)$^+$
47	 HCl	NMR(DMSO-d_6): δ:1.21 - 1.28(6H, m), 6.80(1H, d, J = 7.9 Hz), 6.85(2H, d, J = 8.8 Hz), 7.03(2H, d, J = 8.8 Hz), 7.14(1H, t, J = 7.9 Hz), 7.24(1H, d, J = 7.8 Hz), 7.86(2H, d, J = 8.3 Hz), 7.92(2H, d, J = 8.8 Hz) FAB-MS(m/z): 503(M+H)$^+$
48	 HCl	NMR(DMSO-d_6): δ:6.73 - 6.88(3H, m), 7.03(2H, d, J = 8.8 Hz), 7.14(1H, t, J = 8.3 Hz), 7.24(1H, dd, J = 1.4 Hz, 8.3 Hz), 7.87(2H, d, J = 8.8 Hz), 7.93(2H, d, J = 8.8 Hz), FAB-MS(m/z): 519(M+H)$^+$
49	 HCl	NMR(DMSO-d_6): δ:2.10 - 2.21(1H, m), 2.23 - 2.37(1H, m), 2.79(3H, d, J = 4.9 Hz), 3.02 - 3.21(2H, m), 3.37 - 3.56(4H, m), 3.66 - 3.95(2H, m), 6.81(2H, d, J = 8.8 Hz), 7.15(2H, s), 7.82(2H, d, J = 8.8 Hz), 7.89(1H, dd, J = 2.6, 8.8 Hz), 8.08(1H, d, J = 8.8 Hz), 8.36(1H, d, J = 2.4 Hz), 9.51(1H, s), 10.33 - 10.63(2H, br), 10.68(1H, s) FAB-MS(m/z): 514(M+H)$^+$
50	 HCl	NMR(DMSO-d_6): δ:2.10 - 2.33(2H, m), 2.79(3H, s), 3.01 - 3.22(2H, m), 3.35 - 3.51(4H, m), 3.65 - 3.79(1H, m), 3.85 - 3.98(1H, m), 6.81(2H, d, J = 8.8 Hz), 7.27(2H, s), 7.82(2H, d, J = 9.3 Hz), 7.89(1H, dd, J = 2.5, 8.8 Hz), 8.08(1H, d, J = 9.2 Hz), 8.36(1H, d, J = 2.9 Hz), 9.60(1H, s), 10.37(1H, brs), 10.44(1H, s), 10.69(1H, s) FAB-MS(m/z): 558, 560(M+H)$^+$
51	 HCl	NMR(DMSO-d_6): δ: 2.22(2H, brs), 2.74(3H, s), 3.00 - 3.60(6H, m), 3.81(2H, brs), 6.82(2H, d, J = 9.3 Hz), 7.10 - 7.25(3H, m), 7.83(2H, d, J = 8.8 Hz), 7.90(1H, dd, J = 2.8 Hz, 9.1 Hz), 8.13(1H, d, J = 8.7 Hz), 8.35(1H, d, J = 2.5 Hz), 9.71(1H, s), 9.95(1H, s), 10.58(1H, s), 10.62 - 10.88(1H, br) FAB-MS(m/z): 480(M+H)$^+$

表3（続き）

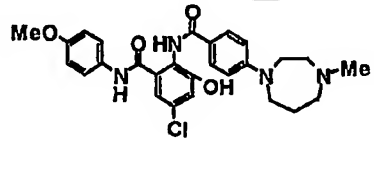
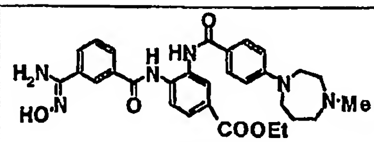
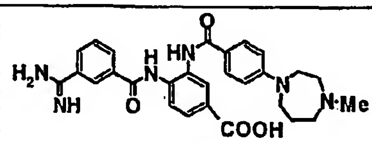
52	 HCl	NMR(DMSO-d_6): δ:2.10 - 2.34(2H, m), 2.81(3H, s), 3.01 - 3.25(2H, m), 3.35 - 3.60(4H, m), 3.62 - 3.79(4H, m), 3.82 - 4.00(1H, m), 6.84(2H, d, J = 9.3 Hz), 6.88(2H, d, J = 8.8 Hz), 7.12(1H, d, J = 2.5 Hz), 7.18(1H, d, J = 2.4 Hz), 7.54(2H, d, J = 9.3 Hz), 7.84(2H, d, J = 8.8 Hz), 9.86(1H, brs), 9.96(1H, s), 10.16(1H, s), 10.43(1H, s) FAB-MS(m/z): 509 $(M+H)^+$
53	 HCl	NMR(DMSO-d_6): δ: 1.35(3H, t, J = 7.3 Hz), 2.79(3H, d, J = 4.9 Hz), 4.36(2H, q, J = 7.3 Hz), 6.85(2H, d, J = 9.3 Hz), 7.68 - 7.74(1H, m), 7.82 - 7.88(2H, m), 7.92 - 7.98(3H, m), 8.19 - 8.24(1H, m), 8.27(1H, s), 8.38 (1H, s) FAB-MS(m/z): 559 $(M+H)^+$
54	 HCl	NMR(DMSO-d_6): δ: 2.79(3H, d, J = 4.9 Hz), 6.85(2H, d, J = 9.3 Hz), 7.76 - 7.84(3H, m), 7.98(2H, d, J = 8.8 Hz), 8.03(1H, d, J = 7.8 Hz), 8.25(1H, s), 8.31(1H, d, J = 7.8 Hz), 8.53(1H, s), FAB-MS(m/z): 515 $(M+H)^+$

表4

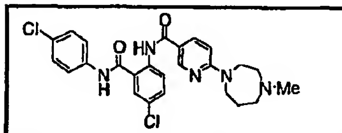
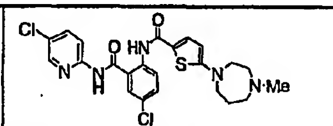
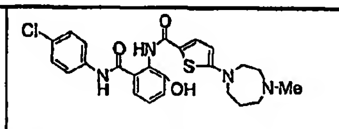
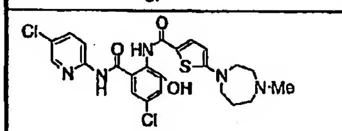
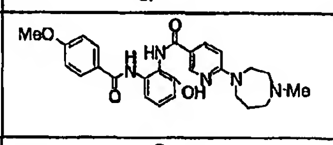
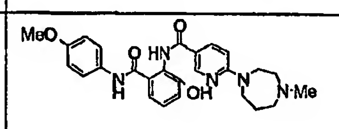
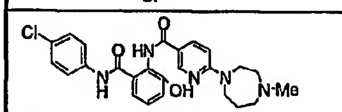
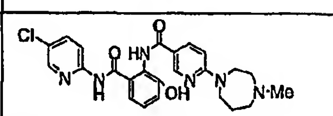
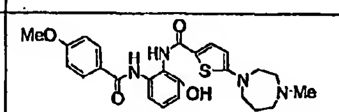
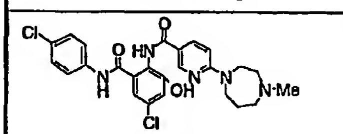
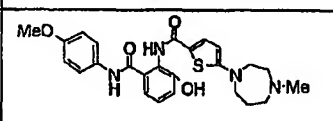
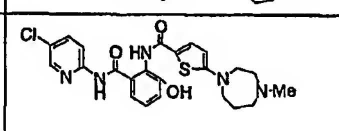
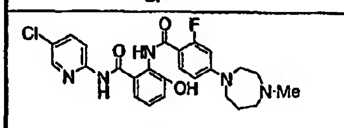
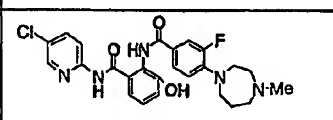
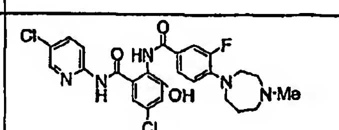
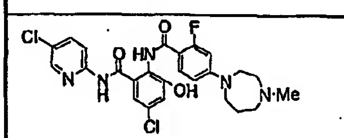
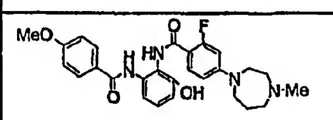
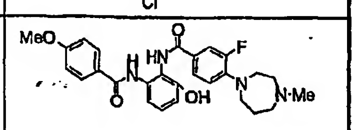
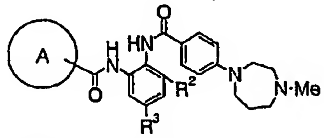
		
		
		
		
		
		

表 5



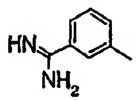
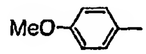
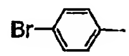
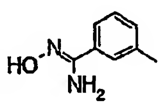
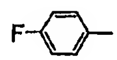
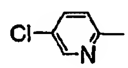
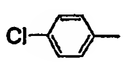
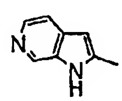
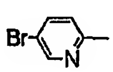
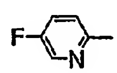
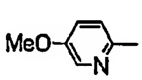
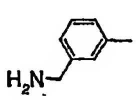
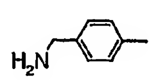
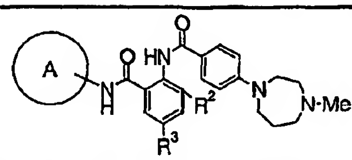
No.	A	R²	R³	No.	A	R²	R³
1		OH	Cl	32		OH	Cl
2		OH	H	33		H	Cl
3		H	Cl	34		OH	Br
4		OH	Br	35		H	Br
5		H	Br	36		OH	Cl
6		OH	F	37		H	Cl
7		H	F	38		OH	Br
8		OH	Cl	39		H	Br
9		OH	H	40		OH	Cl
10		H	Cl	41		H	Cl
11		OH	Br	42		OH	Br
12		H	Br	43		H	Br
13		OH	F	44		OH	Cl
14		H	F	45		H	Cl
15		OH	Cl	46		OH	Br
16		H	Cl	47		H	Br
17		OH	Br	48		OH	H
18		H	Br	49		OH	Cl
19		OH	Cl	50		H	Cl
20		H	Cl	51		OH	Br
21		OH	Br	52		H	Br
22		H	Br	53		OH	H
23		OH	H	54		OH	Cl
24		OH	Cl	55		H	Cl
25		H	Cl	56		OH	Br
26		OH	Br	57		H	Br
27		OH	H	58		OH	H
28		OH	Cl	59		OH	Cl
29		OH	H	60		OH	H
30		H	Cl	61		H	Cl
31		OH	Br	62		OH	Br

表5（続き）



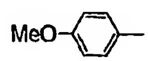
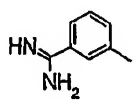
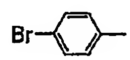
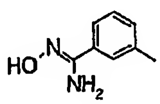
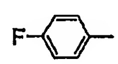
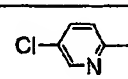
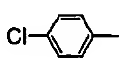
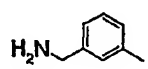
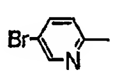
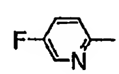
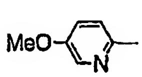
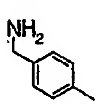
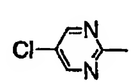
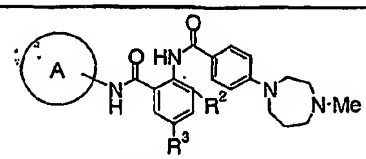
No.	A	R²	R³	No.	A	R²	R³
121		OH	Cl	151		H	Cl
122		OH	H	152		OH	Br
123		H	Cl	153		H	Br
124		OH	Br	154		OH	F
125		H	Br	155		OH	Cl
126		OH	F	156		H	Cl
127		H	F	157		OH	Br
128		OH	Cl	158		H	Br
129		OH	H	159		OH	Cl
130		H	Cl	160		H	Cl
131		OH	Br	161		OH	Br
132		H	Br	162		H	Br
133		OH	Cl	163		H	Br
134		H	Cl	164		OH	F
135		OH	Br	165		OH	Cl
136		H	Br	166		H	Cl
137		OH	Cl	167		OH	Br
138		H	Cl	168		H	Br
139		OH	Br	169		OH	H
140		H	Br	170		OH	Cl
141		OH	H	171		H	Cl
142		OH	Cl	172		OH	Br
143		H	Cl	173		H	Br
144		OH	Br	174		OH	H
145		H	Br	175		OH	F
146		OH	H	176		OH	Cl
147		OH	Cl	177		H	Cl
148		OH	H	178		OH	Br
149		OH	Br	179		H	Br
150		H	Cl	180		OH	H

表５（続き）



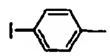
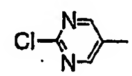
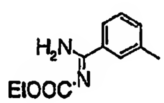
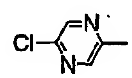
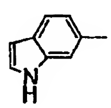
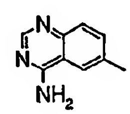
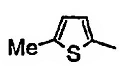
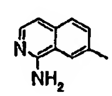
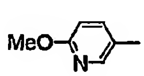
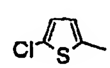
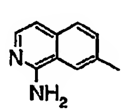
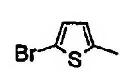
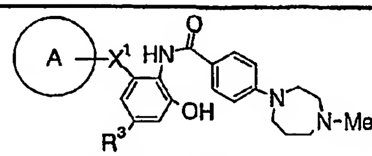
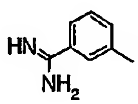
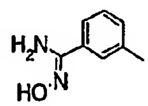
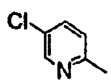
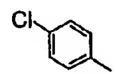
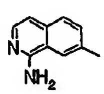
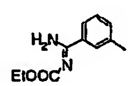
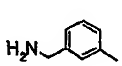
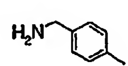
No.	A	R²	R³	No.	A	R²	R³
181		OH	Cl	211		OH	Cl
182		OH	H	212		OH	H
183		H	Cl	213		H	Cl
184		OH	Br	214		OH	Br
185		H	Br	215		H	Br
186		OH	Cl	216		OH	Cl
187		OH	H	217		OH	H
188		H	Cl	218		H	Cl
189		OH	Br	219		OH	Br
190		H	Br	220		H	Br
191		OH	Cl	221		OH	Cl
192		OH	H	222		OH	H
193		H	Cl	223		H	Cl
194		OH	Br	224		OH	Br
195		H	Br	225		H	Br
196		OH	Cl	226		OH	Cl
197		OH	H	227		OH	H
198		H	Cl	228		H	Cl
199		OH	Br	229		OH	Br
200		H	Br	230		H	Br
201		OH	Cl	231		OH	Cl
202		OH	H	232		H	Cl
203		H	Cl	233		OH	Br
204		OH	Br	234		H	Br
205		H	Br	235		OH	H
206		OH	Cl	236		OH	Cl
207		OH	H	237		H	Cl
208		H	Cl	238		OH	Br
209		OH	Br	239		H	Br
210		H	Br	240		OH	H

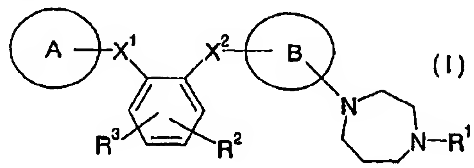
表6



No	A	X^1	R^3	No	A	X^1	R^3
1		$-CH_2-CH_2-$	H	32		$-CH_2-CH_2-$	H
2		$-CH_2-CH_2-$	Cl	33		$-CH_2-CH_2-$	Cl
3		$-NH-CH_2-$	H	34		$-NH-CH_2-$	H
4		$-NH-CH_2-$	Cl	35		$-NH-CH_2-$	Cl
5		$-O-CH_2-$	H	36		$-O-CH_2-$	H
6		$-O-CH_2-$	Cl	37		$-O-CH_2-$	Cl
7		(E) -CH=CH-	H	38		(E) -CH=CH-	H
8		(E) -CH=CH-	Cl	39		(E) -CH=CH-	Cl
9		$-CH_2-CH_2-$	H	40		$-CH_2-CH_2-$	H
10		$-CH_2-CH_2-$	Cl	41		$-CH_2-CH_2-$	Cl
11		$-NH-CH_2-$	H	42		$-NH-CH_2-$	H
12		$-NH-CH_2-$	Cl	43		$-NH-CH_2-$	Cl
13		$-O-CH_2-$	H	44		$-O-CH_2-$	H
14		$-O-CH_2-$	Cl	45		$-O-CH_2-$	Cl
15		(E) -CH=CH-	Cl	46		(E) -CH=CH-	Cl
16		$-CH_2-CH_2-$	H	47		$-CH_2-CH_2-$	H
17		$-CH_2-CH_2-$	Cl	48		$-CH_2-CH_2-$	Cl
18		$-NH-CH_2-$	H	49		$-NH-CH_2-$	H
19		$-NH-CH_2-$	Cl	50		$-NH-CH_2-$	Cl
20		$-O-CH_2-$	H	51		$-O-CH_2-$	H
21		$-O-CH_2-$	Cl	52		$-O-CH_2-$	Cl
22		(E) -CH=CH-	H	53		(E) -CH=CH-	H
23		(E) -CH=CH-	Cl	54		(E) -CH=CH-	Cl
24		$-CH_2-CH_2-$	H	55		$-CH_2-CH_2-$	H
25		$-CH_2-CH_2-$	Cl	56		$-CH_2-CH_2-$	Cl
26		$-NH-CH_2-$	H	57		$-NH-CH_2-$	H
27		$-NH-CH_2-$	Cl	58		$-NH-CH_2-$	Cl
28		$-O-CH_2-$	H	59		$-O-CH_2-$	H
29		$-O-CH_2-$	Cl	60		$-O-CH_2-$	Cl
30		(E) -CH=CH-	H	61		(E) -CH=CH-	H
31		(E) -CH=CH-	Cl	62		(E) -CH=CH-	Cl

Patent Claims.

1. Diazepane derivatives or salts thereof represented by following general formula (I).



(I)

(The symbols in above formula have the following meanings.

A ring and B ring: may be the same or different and denote aryl or heteroaryl each of which may have 1-3 substituents,

X1: -C(=O)=NR4-, -NR4-C(=O)-, -NR4-CH2-, -O-CH2-, -CH2-CH2, or -CH=CH-,

X2: -C(=O)=NR5-, or -NR5-C(=O)-,

R1: hydrogen atom, lower alkyl, -lower alkylene-O-lower alkyl, C3-8 cycloalkyl, aryl, heteroaryl, -lower alkylene-C3-8 cycloalkyl, -lower alkylene-aryl, -lower alkylene-heteroaryl, or -C(=NR6)-lower alkyl,

R2: -OH, -O-lower alkyl, -O-lower alkylene-OH, -O-SO2-OH, -O-lower alkylene-COOH, O-lower alkylene-COO-lower alkyl, -COOH, -COO-lower alkyl, or halogen atom,

R3: hydrogen atom, halogen atom, or lower alkyl,

R4, R5, and R6: may be the same or different and denote hydrogen atom, or lower alkyl)

2. Diazepane derivatives or salts thereof in accordance with Claim 1, wherein R2 is -OH.

3. Diazepane derivatives or salts thereof in accordance with Claim 1, wherein the A ring and B ring are the same or different, and comprise benzene ring, pyridine ring, naphthalene ring, thiophene ring, benzofuran ring or the quinoline ring each of which may have 1-3 substituents.

4. Diazepane derivatives or salts thereof in accordance with Claim 1, wherein the substituent of aryl or heteroaryl each of which may have 1-3 substituents comprises substituents selected from optionally substituted lower alkyl, lower alkenyl, lower alkynyl, C3-8 cycloalkyl, -O-optionally substituted lower alkyl, halogen atom, -NH2, -NH-lower alkyl, -N-(lower alkyl)2, -C(=NH)-NH2, -C(=N-OH)-NH2, -C(=NH)-NH-OH, -C(=NH)-NH-C(=O)-O-lower alkyl, -COOH, -C(=O)-O-optionally substituted lower alkyl, -C(=O)-O-optionally substituted C6-14 aryl, -C(=O)-O-optionally substituted heteroaryl, -CN, -NO2, -OH, -O-CO-optionally substituted lower alkyl, -O-CO-NH2, -O-CO-NH-lower alkyl, -O-CO-N-(lower alkyl)2, -SH, -C(=O)-NH2, -C(=O)-NH-(lower alkyl), -C(=O)-N-(lower alkyl)2.

5. Diazepane derivatives or salts thereof in accordance with Claim 1, which are selected from 3-hydroxy-4'-methoxy-2-{[4-(4-methyl-1,4-diazepan-1-yl) benzoyl] amino} benzanilide, 3-hydroxy-N1-(4-methoxybenzoyl)-N2-[4-(4-methyl-1,4-diazepan-1-yl) benzoyl]-1,2-phenylenediamine, 5-chloro-N-(5-chloro-2-pyridyl)-3-hydroxy-2-{[4-(4-methyl-1,4-diazepan-1-yl) benzoyl] amino} benzamide, 5-chloro-3-hydroxy-4'-methoxy-2-{[4-(4-methyl-1,4-diazepan-1-yl) benzoyl] amino} benzanilide, 5-bromo-N-(5-chloro-2-pyridyl)-3-hydroxy-2-{[4-(4-methyl-1,4-diazepan-1-yl) benzoyl] amino} benzamide.

6. Medicinal composition containing diazepane derivatives or salts thereof described in Claim 1 as effective ingredient.

7. Activated blood coagulating factor X inhibitor containing diazepane derivatives or salts thereof described in Claim 1 as effective ingredient.

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